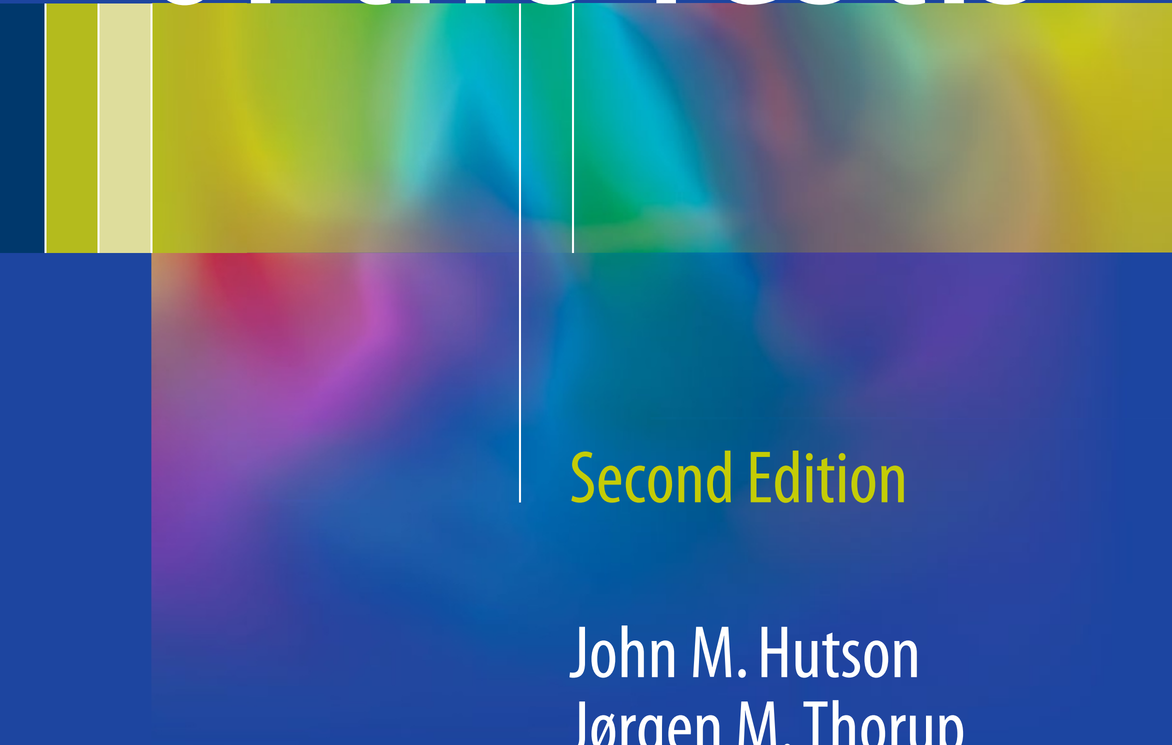
Descent of the Testis



Second Edition

John M. Hutson
Jørgen M. Thorup
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Preface

Descent of the testis, or lack thereof, is a subject of great controversy in embryology, endocrinology, and paediatric surgery. For such a common abnormality as undescended testis, it is surprising that there still remain so many unanswered questions, more than 20 years after our first edition (Table 1).

This book aims to present up-to-date evidence from our own and other laboratories of the normal mechanisms of testicular descent (Chaps. 2 and 3), along with a brief description of the evolution of descent and the early history of research into its cause (Chap. 1).

Chapters 4–10 describe the clinical problems of undescended testes and give our own, necessarily biased, opinion of the best ways to diagnose and treat the anomaly. We have not emphasised hormonal treatment, which has been vigorously proposed by others in recent years, for two major reasons. First, current evidence now suggests that direct or indirect stimulation of androgen secretion only causes relaxation of the cremaster muscle in “retractile” testes, but has little effect on truly undescended testes. Second, luteinising hormone-releasing hormone (LHRH) or its long-acting analogues have not been approved for clinical use in Australia, and one of the authors (JMH) has no direct experience of their use. Human chorionic gonadotrophin (hCG) is available, but is not in general use because of lack of efficacy and the need for a significant number of painful injections. Buserelin (LHRH analogue) is in use in some parts of Europe, but its efficacy remains very controversial.

The descriptions of the clinical diagnosis (Chap. 7) and the surgical treatment (Chap. 8) are given in detail, with extensive pictorial support, so as to give the trainee surgeon enough information to be able to learn exactly what we do. We have opted for a detailed description of orchidopexy as it is performed currently. Previous surgical techniques have been omitted deliberately because they were cruel, unnecessary, or caused testicular atrophy. There is now no place for such methods in modern paediatric surgery, where the goal is to perform day-case surgery with minimal pain or discomfort to the hapless infant or child. With this approach, orchidopexy can be performed without any painful injections or unpleasant memories.

Table 1 Questions needing answers about testicular descent

Why does the testis descend?
How does the testis descend?
What causes undescended testes?
What is the best treatment for maldescent?
Does hormone therapy have a role in treatment and/or diagnosis?
Are there any new alternatives to surgical treatment?
When is the optimal time for treatment?
Are “retractile” testes normal or abnormal?
Do retractile/ascending testes need treatment?
What is the cause of infertility and increased malignancy?
Will fertility improve and the risk of cancer diminish with current modes of treatment?

The long-term results of current surgical treatment (Chap. 10) remain unknown, but we are optimistic that surgery in infancy will lead to a significant improvement in fertility and reduced risk of malignancy.

Chapter 11 concludes this short monograph with an attempt to summarise our answers to the list of questions given above. Inevitably, some of our answers will be found wanting in the future, but they will serve as a guide to future advances. Finally, we speculate on the ways that undescended testes may be treated in the future, based on our research into normal mechanisms of descent and the physiology of the testis.

There are many areas of the subject that we have not dealt with extensively; the reader should consult those books that address these areas directly. For a classic description of the human problems, the reader could do no better than read Scorer and Farrington’s 1971 treatise [1]: we have attempted unashamedly to emulate its style and approach. During the 1970s and early 1980s, the dominant paradigm was the central role of the hypothalamic-pituitary-gonadal axis which provided the rationale for hormone treatment. Several good multi-authored volumes appeared at that time, with extensive discussion of all endocrine aspects of the problem [2–7]. The role of hormones in treatment was questioned in 1986 by de Muinck Keizer-Schrama and Hazebroek in their joint thesis from Erasmus University, Rotterdam [8].

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Evolution of Descent of the Testis and Early History of Research

1

1.1 Evolution of Testicular Descent

1.1.1 Why Is the Testis Descended at All?

Early vertebrates had intra-abdominal gonads, regardless of sex. With subsequent evolution of sexual differences in mammals and marsupials, the testis has acquired a different position from the ovary, presumably because this different position has conferred some biological advantage. It is not known exactly why evolution has produced descended testes outside the abdominal cavity, although there is little doubt that the scrotum has become a highly specialised, low-temperature environment. Bedford [1] proposed that descent of the testis is a secondary phenomenon accompanying descent of the epididymis. Since early vertebrates, such as fish, probably ejaculated the semen into the environment, spermatozoa may have acquired advantage by being adapted to environmental temperatures below that of the body: the caudal epididymis, which stores spermatozoa, also might benefit from adaptations to cooler temperatures. In animals where the testis is not normally descended into a pendulous scrotum, the caudal epididymis is the most superficial genital organ and hence is maintained at a lower temperature than the internal organs. The testis which produces spermatozoa also may have acquired evolutionary advantage from being at a lower temperature.

Most mammals have acquired numerous sophisticated anatomical and physiological adaptations of the scrotum to keep the epididymis and testis cool (Table 1.1), many of which are present in the human. Because the human testis has inherited major adaptations fitting it to exist at a lower temperature than the body core, any disruption of normal descent would be expected to upset testicular physiology, as is discussed in Chap. 6.

The different anatomical and physiological characteristics found in different species are important for an overall understanding of human testicular descent because they reveal the various phases through which the mechanism has passed. Some of these phases may be concealed by idiosyncratic anatomical features, but the basic mechanism of testicular descent should be present in increasing complexity.

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Table 1.1 The scrotum as a low-temperature environment

Character	Physiological role
Thin, pigmented skin	Heat loss by conduction/radiation
No subcutaneous fat	Heat loss by conduction
Absent hair/fur (e.g. bull/rat)	Heat loss over caudal epididymis
Pampiniform plexus	Countercurrent heat exchange
Cremaster muscle	Controls testicular position in response to external temperature
Dartos muscle	Controls scrotal dependency in response to external temperature
Fat pad in inguinal canal (e.g. rat)	Insulates testis from abdominal cavity
Fat pad between testis and epididymis (rat)	Insulates caudal epididymis from testis
Processus vaginalis closure (primates)	Keeps testis outside abdominal cavity

1.1.2 Which Animals Have Descended Testes?

Descent of the testis from its initial intra-abdominal position on the ventromedial aspect of the urogenital ridge to an external, subcutaneous scrotum occurs only in mammals. Other vertebrates, such as fish and birds (Fig. 1.1), have testes which remain inside the abdomen. Monotremes, such as the platypus and the spiny anteater or echidna (Fig. 1.2), form an intermediate group between mammals and other vertebrates and have high, intra-abdominal testes [2]. By contrast with the platypus and echidna, modern marsupials such as the kangaroo exhibit complete testicular descent to an external scrotum, albeit in the groin rather than the perineum (Fig. 1.3) [3, 4].

Some eutherian mammals have intra-abdominal testes which remain in their original position on the urogenital ridge. These include such widely different animals as the elephant and the rock hyrax (a small African herbivore) [5] (Fig. 1.4). The elephant (Fig. 1.5) and the hyrax appear to have no structure analogous to the gubernaculum. Aquatic mammals (porpoises, dolphins, and whales) have testes which are partially descended within the abdomen [6, 7] (Fig. 1.6a, b). Meek has speculated that aquatic mammals had descended testes during an earlier epoch, but this feature has been lost to a variable extent in subsequent millennia.

In the narwhale (Fig. 1.6c) [7] and the prairie dog [8] (Fig. 1.7), the testes are lateral to the bladder neck, just inside the inguinal region. Hedgehogs, moles, and shrews have testes lying lateral to the bladder; in spring and presumably in response to a surge of androgens, the enlarged testes protrude temporarily into sacs near the base of the tail [9] (Fig. 1.8). Sloths and armadillos have testes between the bladder and rectum [10].

The testes of the chinchilla are just inside the inguinal aperture, but the caudal epididymis protrudes into a thin-walled scrotal diverticulum [11] (Fig. 1.9). Some animals have testes in a subcutaneous pouch which communicates freely with the peritoneum, as is the norm for rats and mice. The southern elephant seal (Mirounga leonina Linnaeus) has two separate inguinal pouches rather than a single scrotum [12].

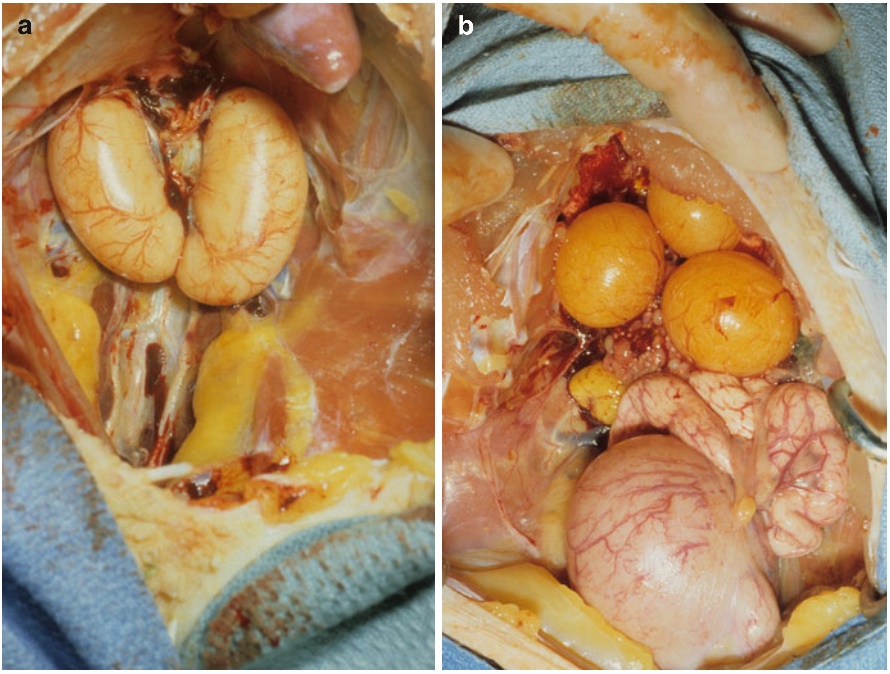

Fig. 1.1 The intra-abdominal gonads of the domestic fowl. (**a**) The large testes are high on the posterior abdominal wall of an adult rooster, near the normal position of kidneys in a mammal. Note that the testes are larger than the heart, shown at the top of the picture. (**b**) The single (*left*) ovary of the hen, showing eggs at various stages of development. The single (*left*) oviduct contains several eggs in transit

Even where a formed scrotum is present, its exact site and degree of development varies widely. The hyaena, for instance, has two posterior shallow scrotal pouches [13], while the kangaroo has a large prepenile scrotum in the groin located directly over the external inguinal rings.

In some mammals, the testicular position relative to the scrotum varies with sexual maturity and season. In the bear, for instance, the testes are scrotal from infancy but are held close to the body, except in the adult during the breeding season, when they are pendulous because of scrotal relaxation. The testes of the rhesus macaque descend prenatally into the scrotum but then reascend to the inguinal canal after birth, only to re-enter the scrotum finally at puberty (Fig. 1.10) [14]. This suggests that the abnormality of ‘ascending’ testes (that descend into the scrotum at puberty) in the human is normal in the macaque.

As can be seen from this brief summary, only a small number of highly specialised mammals have no testicular descent, e.g. monotremes, hyrax, elephant, and possibly some insectivores. Partial intra-abdominal descent occurs in the Cetacea (porpoises, dolphins, and whales). The testis is inguinal in position in edentates, some insectivores, and some ungulates; these animals probably have ancient origins, despite their highly specialised characteristics. Other animals have a subcutaneous pouch rather than a true scrotum and exhibit periodic or seasonal descent of the testes.

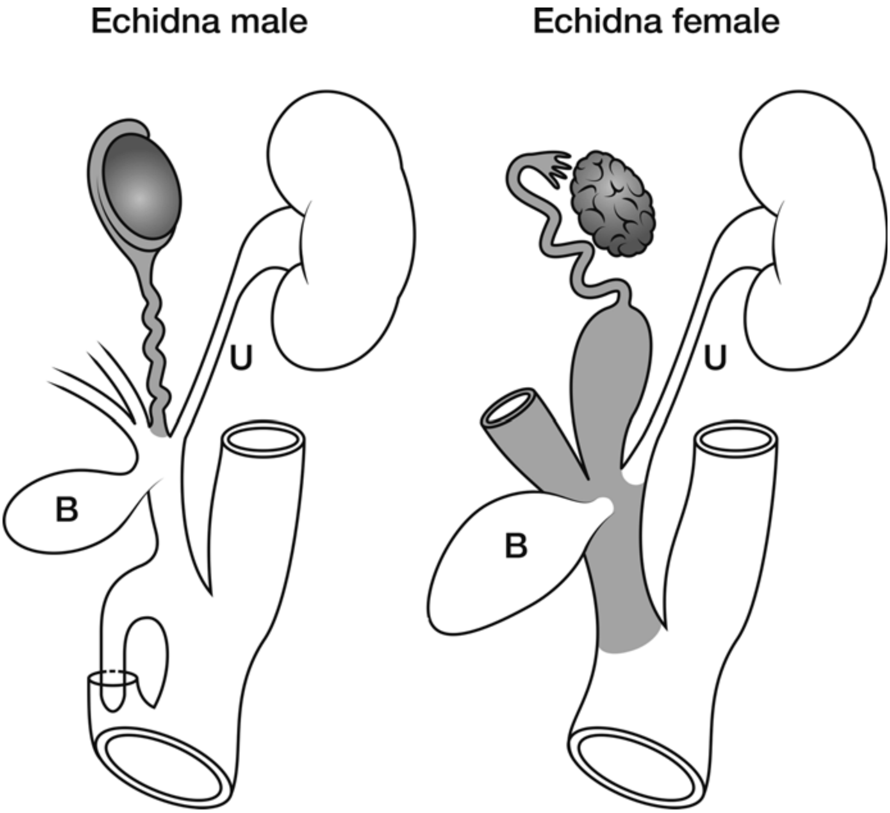

Fig. 1.2 Gonadal position in the monotreme echidna. The testes and ovaries are in a similar intra-abdominal position near the kidneys (Redrawn from Renfree [43]). *B* bladder, *U* ureter

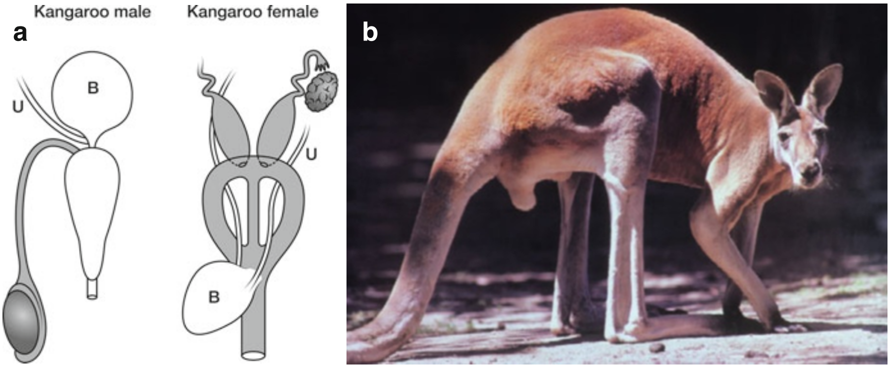

Fig. 1.3 Gonadal position in the marsupial kangaroo. (**a**) In the male, the testis is fully descended into a prepenile scrotum, while in the female, the ovary remains near the kidney. (**b**) The male red kangaroo, showing the descended testes in the scrotum in the inguinal region, in front of the penis

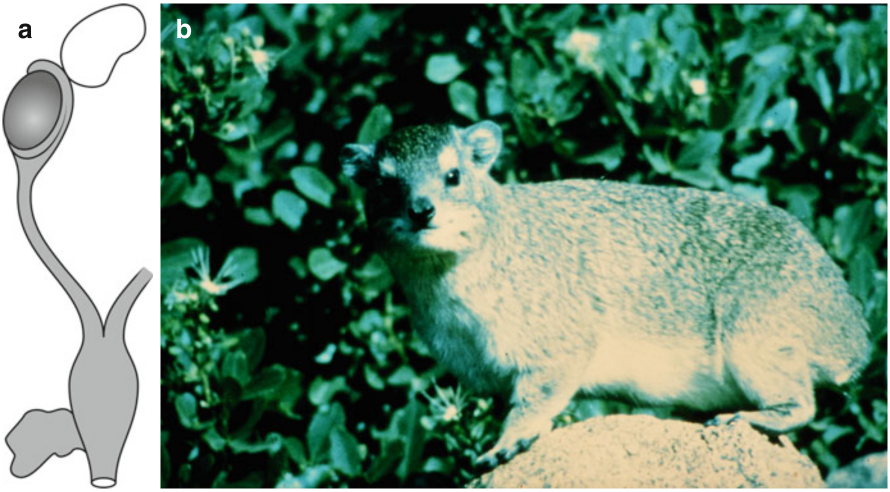

Fig. 1.4 (**a**) The testicular position in the rock hyrax (Redrawn from Williams and Hutson [4]). (**b**) The rock hyrax, a small herbivore living in rocky outcrops in parts of Africa and one of the few mammals where the testes are in the same position as ovaries

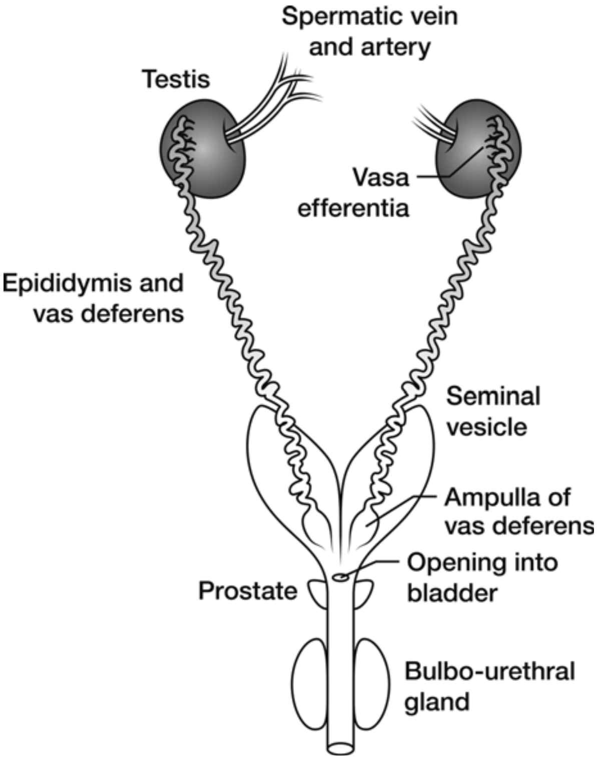

Fig. 1.5 The intra-abdominal testes of the African elephant (Reproduced with permission from Short et al. [44])

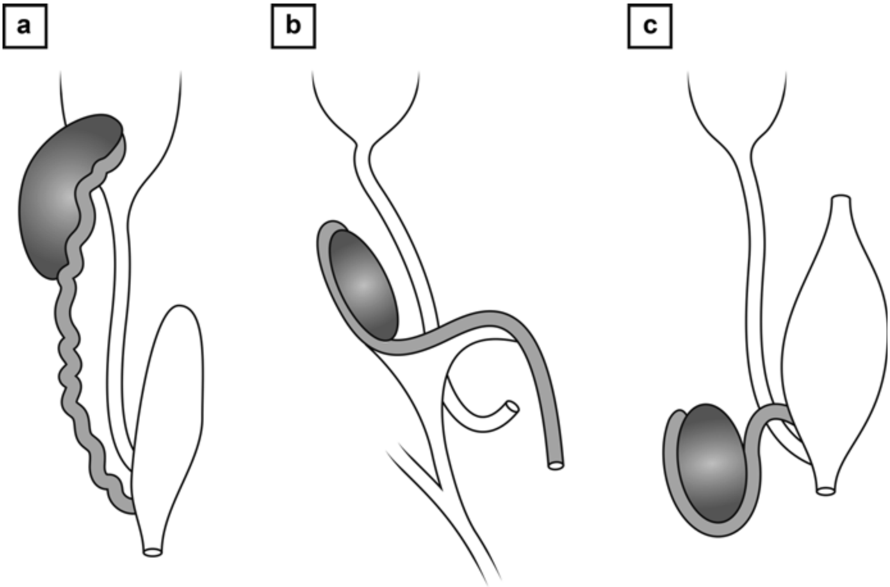

Fig. 1.6 Aquatic mammals (Cetacea), such as (**a**) the porpoise, (**b**) the fin whale, or (**c**) the narwhale, have testes that descended to a variable extent but are still intra-abdominal (Redrawn from Williams and Hutson [4])

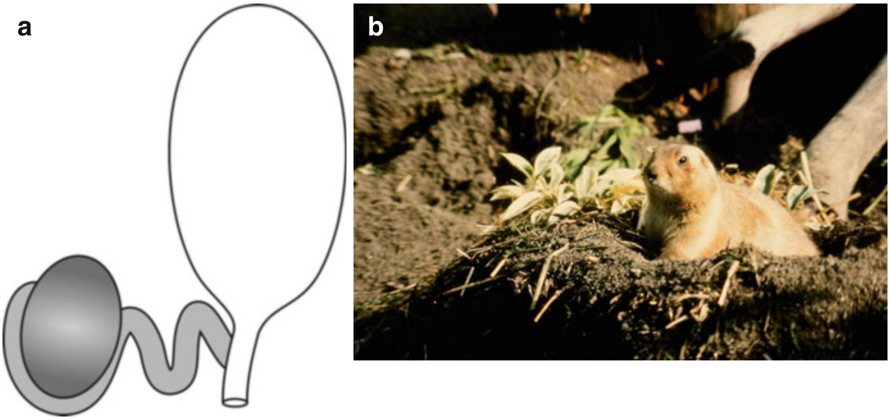

Fig. 1.7 (**a**) The prairie dog has testes that have descended down to beside the bladder neck. (**b**) The prairie dog emerging from its burrow (Photo courtesy of the Royal Melbourne Zoo)

In the large number of modern mammals, e.g. marsupials, ungulates, carnivores, and primates, the testes have descended permanently into a definite scrotum (Fig. 1.11), which in many mammals is located in the same place (i.e. just outside the inguinal canal) as the mammary glands. While life-long patency of the processus vaginalis that enables retraction of the testes back into the abdomen is normal in rodents, the processus vaginalis of apes and humans has become obliterated.

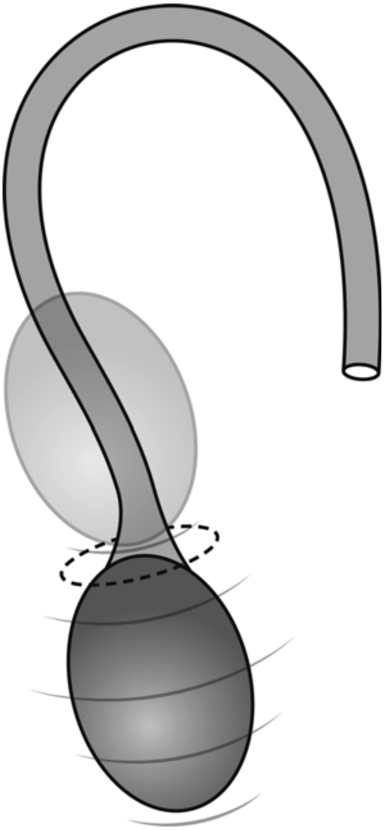

Fig. 1.8 The testis of the tree shrew is located inside the inguinal canal but can descend into a subcutaneous pouch (Redrawn from Williams and Hutson [4])

During evolution, the testes have migrated from their initial position in the embryonic urogenital ridge, which in most species is revealed in the adult by the position of the ovary. As there are a small number of mammalian species with testes in the same position as the ovary and a large number with testes in the inguinal region, it would appear that descent to the inguinal region is the first evolutionary phase of descent. It is likely that these animals evolved a mechanism for testicular descent to this point by growth of the gubernaculum [15]. Because the more-recently evolved mammals have testes outside the inguinal abdominal wall in a specialised scrotum, we can assume that further descent from the inguinal region offered further evolutionary advantage. In addition, migration of the testis beyond the inguinal region is related to migration of the gubernaculum, which is a process that is completely different from the gubernacular enlargement seen in intra-abdominal migration.

1.1.3 Stepwise Descent of the Testis

The stepwise descent of the testis during mammalian evolution parallels the stepwise descent seen in the modern mammalian fetus, such as the mouse and the human

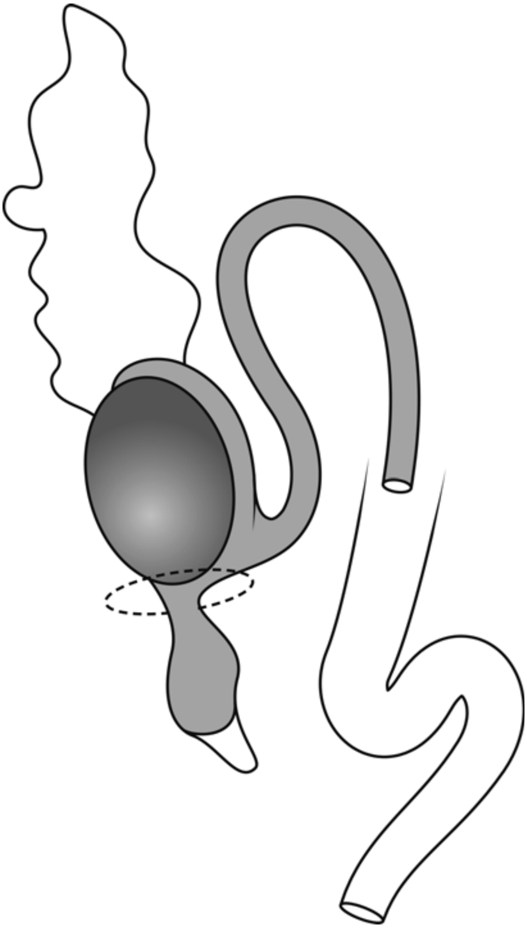

Fig. 1.9 The chinchilla's testis is just inside the inguinal ring, but the caudal epididymis protrudes through. There is a fat pad on the top of the epididymis, and the vas deferens joins the back of the lower urinary tract (Redrawn from Williams and Hutson [4])

[16]. Between about weeks 10 and 15 of gestation in the human, the testis remains close to the future internal inguinal ring because the enlarging gubernaculum in the male acts as an anchor. On the other hand, the gubernaculum in the female fetus remains thin and tenuous, and the ovary (in most species but not the human) shifts away from the inguinal region as the fetus enlarges [17]. The elongation of the thin gubernaculum to form a round ligament in the female is the reverse of the broad, short gubernaculum in the male that remains at a fixed length. Around 25–28 weeks gestation, the testis descends rapidly through the inguinal canal and then migrates more slowly from the external inguinal ring to the scrotum, arriving there at 35–40 weeks. This phase of descent is preceded by migration of the gubernaculum from the inguinal canal to the scrotum.

The stepwise descent of the testis observed in human embryos and laboratory animals led to the concept that testicular descent may occur in two or more phases. This concept was proposed initially by Wensing [15, 18] and one of the

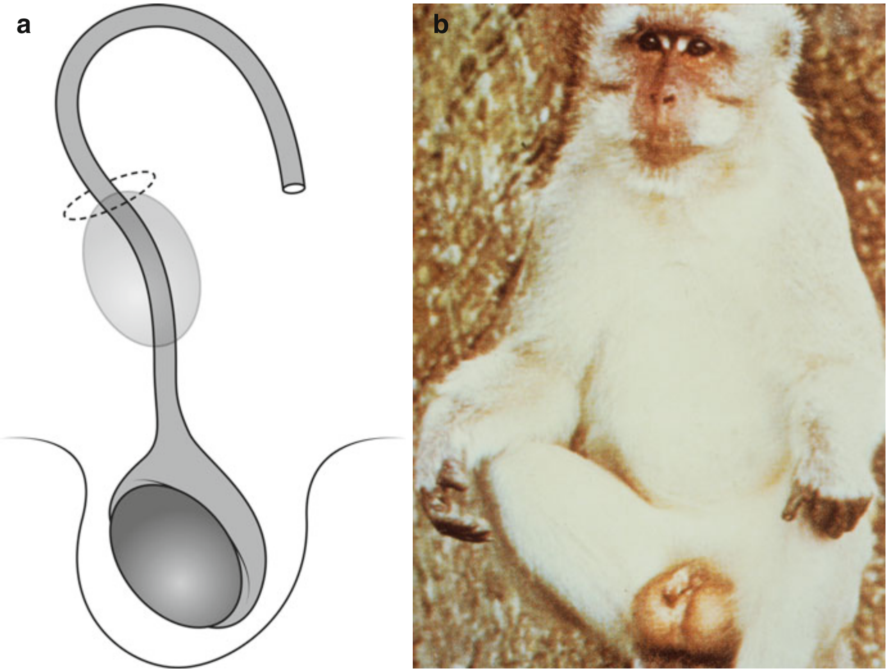

Fig. 1.10 (**a**) In the macaque, the testis descends into a scrotum at birth but then ascends to the groin until puberty, when permanent descent occurs. This animal shows that 'ascending testis' with final descent at puberty can be normal, as compared to the human where it is abnormal (Reproduced with permission from Ref. [14]). (**b**) An albino adult male macaque, showing the scrotal position of the testes (Photo courtesy of the Royal Melbourne Zoo)

authors [19, 20]. Wensing's observations of the enlargement (or 'swelling reaction') of the male gubernaculum in the pig fetus and other species, coupled with observations of rodents by Habenicht and Neumann [18], suggested that testicular descent was not only stepwise morphologically but also stepwise in its hormonal control. The naturally occurring mutation in the androgen receptor gene in the testicular feminising (TFM) mouse, in which the androgen receptor is completely non-functional, provided crucial evidence for stepwise testicular descent because no tissues in this mouse are able to respond to circulating androgens [19]. In this animal the swelling reaction of the gubernaculum occurs relatively normally, and the testis resides near the inguinal region beside the bladder neck, but no migration outside the abdomen occurs. The explanation was that androgens are required for migration from the groin to the scrotum, but that other hormonal factors control intra-abdominal migration and enlargement of the gubernaculum [19].

The detailed evidence for multiphasic testicular descent, both morphological and hormonal, is discussed in Chaps. 2 and 3: here we summarise some of the historical evidence which has been accumulated over the last two centuries [3, 4].

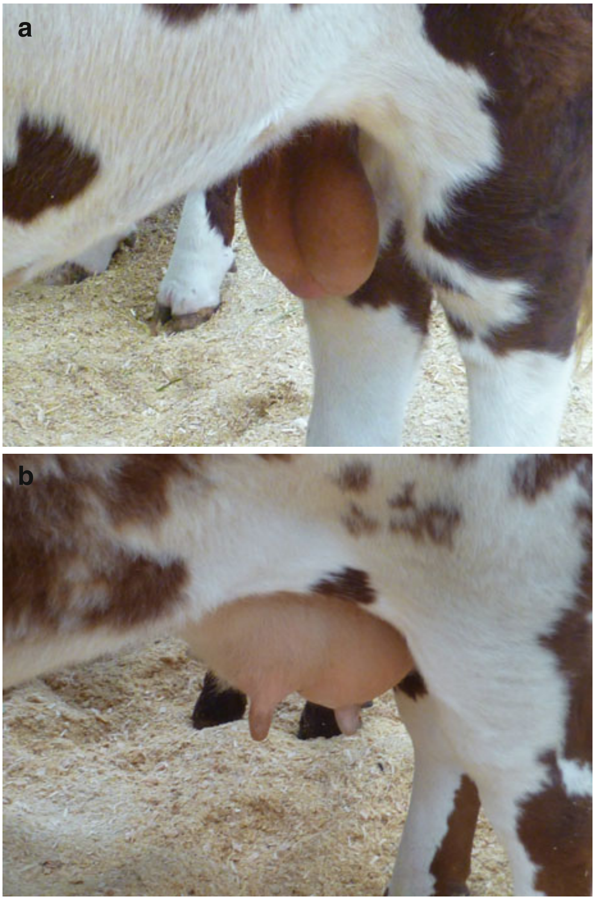

Fig. 1.11 The testis in ungulates descends into a pendulous scrotum before birth. (**a**) In this prize bull, the hairless scrotum is quite conspicuous and is located in the same anatomical site as the mammary glands in a cow (**b**)

1.2 Early Work on Testicular Descent

1.2.1 The Role of the Gubernaculum

The study of testicular descent began in earnest with the observations of John Hunter [21] (Fig. 1.12). In 1762 and 1786, he described the fetal testis and epididymis in the abdomen and provided the first accurate description of the gubernaculum. He found that the fetal testis was connected to the abdominal wall by a ligament, or so-called gubernaculum testis, because it appeared to direct the course of the testis during descent. Hunter thought that the gubernaculum was vascular and fibrous and covered by fibres of the cremaster muscle.

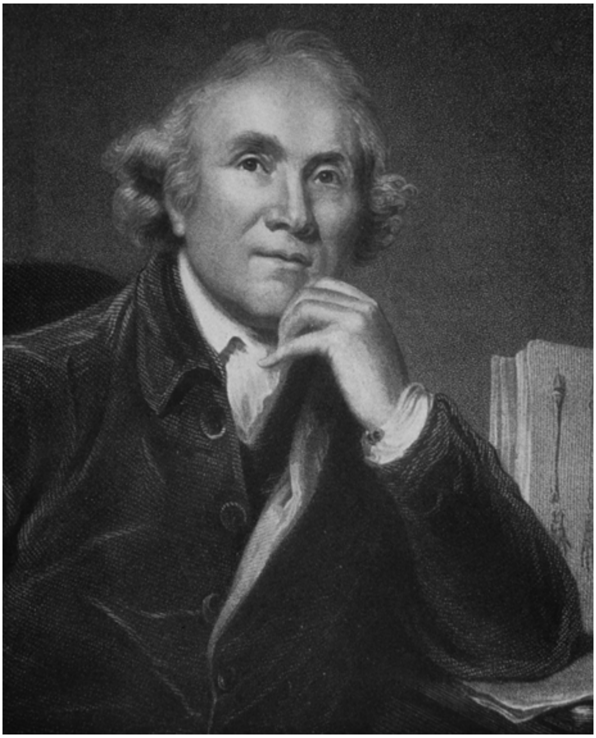

Fig. 1.12 John Hunter, Scottish surgeon–scientist, who first described the gubernaculum. A close up from an engraving by G.H. Adcock, based on a painting by Sir Joshua Reynolds

The relationship between the gubernaculum and the developing cremaster muscle within it was the subject of much controversy, in part related to anatomical differences between species. Seiber [22] described ascending muscular fibres in the gubernaculum by extrapolation from dissections of adult non-human mammals. Curling [23] described the gubernaculum as a soft, solid cone which varies in shape and size at different stages of descent. He found a bulky central part composed of primitive cellular tissue (i.e. embryonic mesenchyme) surrounded by a layer of muscular fibres and another layer of 'mesenchyme', the whole being invested by peritoneum except posteriorly. Cloquet and Carus [24, 25] believed that the cremaster was formed mechanically from the passage of the testis through the abdominal wall, which pulled loops of muscle fibres off the conjoint tendon made up of the *internal oblique* and *transversus abdominis* muscles.

Migration of the gubernaculum from the inguinal region to the scrotum was well recognised in the nineteenth century. Cleland [26] dissected human fetuses of 5 and 6 months' gestation and found that the fetal gubernaculum ended in the inguinal abdominal wall and did not extend directly from the testis to the scrotum. Hence, the alternative name for the gubernaculum became the genito-inguinal ligament. Cleland believed that the gubernaculum migrated ahead of the testis into the scrotum, creating a space lined by peritoneum. He did not think that the cremaster muscle pulled the testis into the scrotum. (It is not surprising that our current understanding of the gubernaculum, as a structure migrating to the scrotum with the testis inside it in the processus vaginalis, is effectively the same as that described by Cleland more than 150 years ago.)

One theory which was popularised by Lockwood [27] was that differential growth of the posterior abdominal wall relative to the pelvis meant that the testis remained stationary while its surroundings grew further apart. Lockwood did not believe that the gubernaculum contracted but imagined that the gubernaculum passively held the testis near the inguinal region. In subsequent years, this passive effect of relative growth was interpreted to mean that this phase of descent was unimportant. However, anchoring of the gonad by the gubernaculum fails to occur in the female fetus, indicating that this effect in the male is hormonally mediated. In fact, in the female fetus, the ovary actually ascends relative to the position it occupied initially in early development.

Lockwood also speculated that the gubernacular muscle must serve some purpose, leading to the idea that the different final location to the testis may be caused by a fan-shaped gubernaculum. Although he was unable to demonstrate these so-called Tails of Lockwood on dissection, he postulated their existence as an explanation for the observation that the gubernaculum becomes attached in a range of different positions [28, 29]. Now that it is known that the gubernaculum actually migrates to the scrotum, the ‘Tails of Lockwood’ should no longer be considered a valid concept [29], and the mechanical phases of testicular descent are better understood (Fig. 1.13).

Coley [30] and Sebileau [31] did not believe that an ectopic position of the testis was caused by an aberrant gubernaculum. Many surgeons and authors believe that an undescended testis or ectopic testis is caused by mechanical obstruction [32–34].

1.2.2 The Role of Hormones

In the early twentieth century, the advent of hormonal studies of sexual development undermined the credibility of previously held mechanical and anatomical concepts [35, 36]. In an effort to ‘explain’ testicular descent in endocrinological terms, these earlier mechanical hypotheses were discarded. Initially, the simplest hormonal concept was that male androgens under pituitary control simply caused testicular descent [37]. This led to attempts to treat boys with undescended testis with crude preparations of human chorionic gonadotrophin (hCG) and, once these steroids had been synthesised, with androgens. Early optimistic reports of success of these treatments were eventually replaced with more realistic and consistently disappointing reports.

1.2.3 Phasic Control

Experimental evidence from the fetus failed to support the idea that testicular descent was controlled by testicular androgens alone [15, 18, 38, 39]. Such

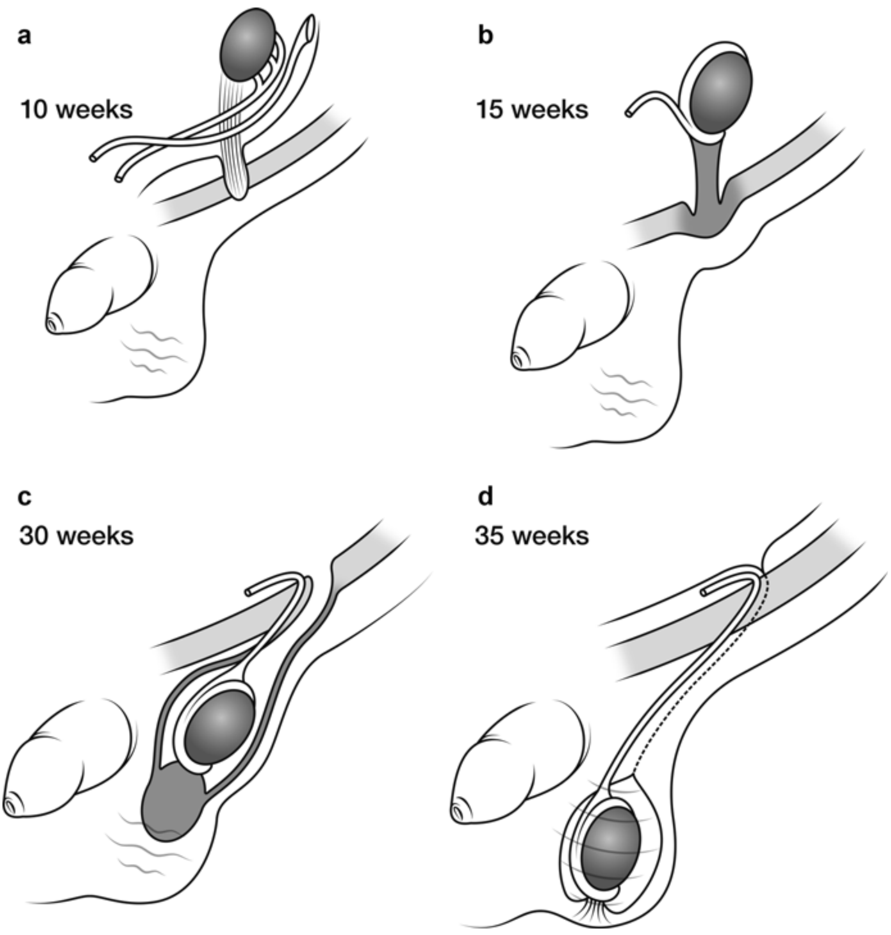

Fig. 1.13 The mechanical steps of testicular descent. Schema showing the testicular position and gubernaculum at different stages of fetal development. (**a**) At 10 weeks the testis is in the urogenital ridge with both Wolffian and Müllerian ducts, and the gubernaculum (genito-inguinal ligament) attaches the testis to the abdominal wall. (**b**) By 15 weeks the Müllerian duct has regressed, and Wolffian duct is developing into an epididymis and vas deferens. The gubernaculum has enlarged, which holds the testis near the future inguinal canal. The processus is beginning to grow into the gubernaculum. (**c**) At 30 weeks the gubernaculum is migrating to the scrotum with the testis inside the processus vaginalis, which is elongating within the gubernaculum so that the intra-abdominal testis can reach the scrotum while still inside the processus vaginalis. (**d**) By 35 weeks migration is usually complete, and the gelatinous gubernaculum has resorbed, leaving the processus vaginalis, which becomes attached to the scrotal skin. The proximal processus obliterates, leaving the testis in a satellite peritoneal cavity (tunica vaginalis) in the hemiscrotum

discrepancies eventually led to the proposal of multihormonal control [40]. Evidence from our own laboratory then suggested that testicular descent occurred in two separate phases, each of which was controlled by different hormones [41], and this is now widely accepted [42] and described in Chaps. 2 and 3.

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Transabdominal Migration of the Testis

2

2.1 The First Phase of Descent

In the 1930s, testicular descent was thought to be controlled by androgens in a single step (Fig. 2.1). In the 1980s, however, opinions diverged about the role of androgens until it was proposed that androgens may have little or no role to play in the initial transabdominal migration of the testes [1, 2]. Then in 1999, it was discovered that the first phase of descent was controlled by the newly identified Leydig cell factor, insulin-like hormone 3 (INSL3).

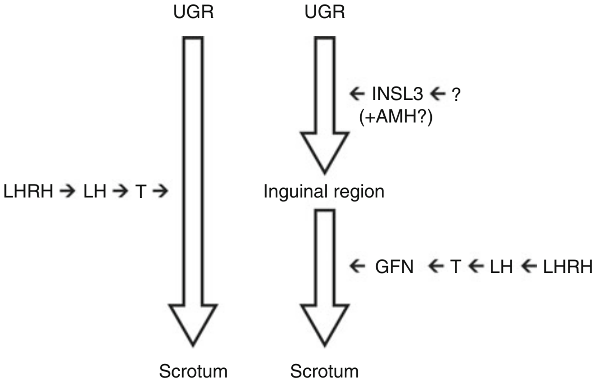

Fig. 2.1 (**a**) The first endocrinological hypothesis to account for testicular descent from the urogenital ridge (*UGR*) to the scrotum. Testicular testosterone (*T*) was stimulated via the hypothalamus (*LHRH*) and pituitary (*LH*) to induce complete descent. (**b**) The two-step endocrinological hypothesis which proposes that testicular descent occurs in two morphologically distinct phases. Control of the first step is by INSL3. The second step is controlled by androgens analogously to the original hypothesis

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Early studies had produced apparently contradictory observations because it was assumed that testicular descent occurred in one step. The authors studying the fetal pig and dog found no convincing role for androgens in testicular descent, whereas those looking at later events with postnatal rats found androgens had a significant effect [3–5]. Moreover, the male fetal mouse exposed to oestrogen [5–9] showed that oestrogen inhibited not only androgen production by the testis but also testicular descent and regression of the Müllerian ducts. The results were interpreted at the time as supporting a role for androgens in testicular descent.

The contradictory conclusions arising from these different model systems led to the proposal in the 1980s that testicular descent may in fact occur in two phases rather than one, each phase being under separate hormonal control [1, 10, 11]. The two-step model of testicular descent is now widely accepted, although some anatomical studies of human embryos and fetuses describe extra steps, some of which occur before the onset of sexual differentiation in the embryo [12].

The first phase involves relative transabdominal descent of the testis compared with the ovary, a common feature of which is enlargement in the male of the gubernaculum, now known as the ‘swelling reaction’ [13].

2.2 The Gubernacular ‘Swelling Reaction’

In the pig fetus, there is enlargement and outgrowth of the caudal end of the gubernaculum, which was associated with early transabdominal migration of the testis [14]. Similarly in the mouse, the testis moves relatively closer to the groin between 15 and 17 days of gestation [9]. This relative movement of the gonad does not occur in the female mouse fetus, where the ovary maintains a constant relationship to the lumbar region (Fig. 2.2) and even appears to ascend in the abdominal cavity relative

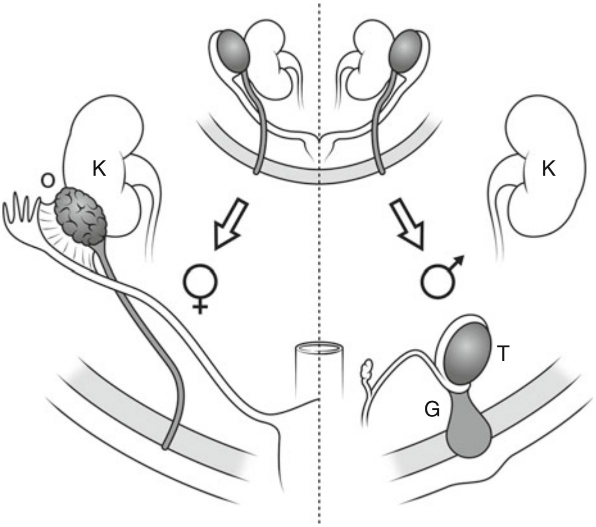


Fig. 2.2 Schema showing the relative movements of the ovary (*O*) and testis (*T*) in the fetal mouse between 14 and 18 days of gestation (*K* kidney, *G* gubernaculum, *T* testis, *O* ovary) (Reproduced with permission from Hutson et al. 1990)

to the inguinal region [15]. The gubernaculum of the female has no swelling reaction and remains thin and cordlike, with elongation of this cord in proportion to fetal enlargement (Fig. 2.2).

Similarly in the human female fetus, there is no swelling reaction, and the gubernacular cord elongates in proportion to the enlarging abdominal cavity to create the round ligament (Fig. 2.3).

In the male, the enlarged gubernaculum anchors the testis close to the inguinal region as the embryo enlarges. The distance between the testis and the inguinal region remains fairly constant but appears to shorten when compared with the distance between the kidney or the ovary and the inguinal region (Fig. 2.4). In the 1940s, this change in testicular position was interpreted as indicating a merely passive role for the gubernaculum [16, 17], when this was the opposite of the actual situation.

The gubernacular swelling reaction is caused by cell division within the fetal gubernaculum, as well as deposition of a significant amount of extracellular matrix [18, 19]. This extracellular matrix is primarily hyaluronic acid and chondroitin sulphate [20]. These matrix molecules are particularly hydrophilic and lead to significant absorption of water into the gubernaculum, giving it an appearance similar to the Wharton's jelly found in the umbilical cord. The swelling reaction is unaffected by experimental manipulation of fetal androgen levels in rodents, pigs, and dogs [10, 13, 21–23]. Also in the fetal pig, raccoon dog, mouse, and human with complete androgen resistance, the gubernacular swelling reaction and transabdominal testicular descent remain essentially normal (Fig. 2.5) [21, 24, 25]. In these animals, the swelling reaction and the gonadal position are initially normal for the male.

Before the discovery of INSL3, some authors proposed that androgens still had a role in gubernacular swelling, despite the contrary evidence cited above. Husmann and McPhaul [26] identified androgen receptors in the mesenchymal core of the

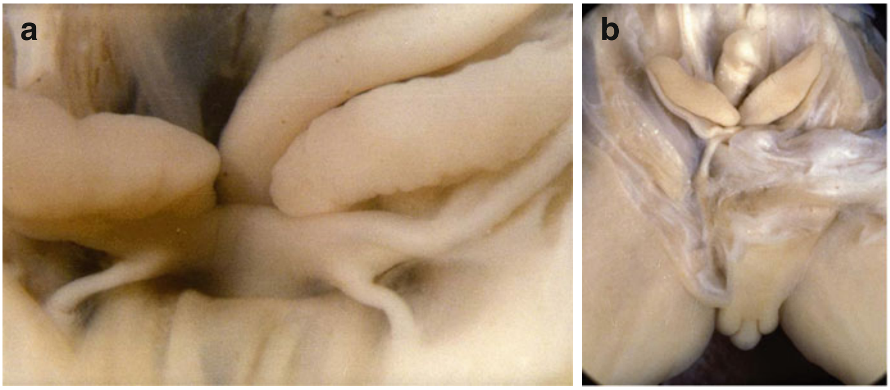


Fig. 2.3 (**a**) Human female fetus at 9 weeks showing the developing ovary and Müllerian ducts in the urogenital ridges and the gubernaculum attaching the ducts and lower poles of the ovaries to the inguinal abdominal wall. (**b**) Human female fetus at 15 weeks showing that the gubernacular cord is elongating into a round ligament

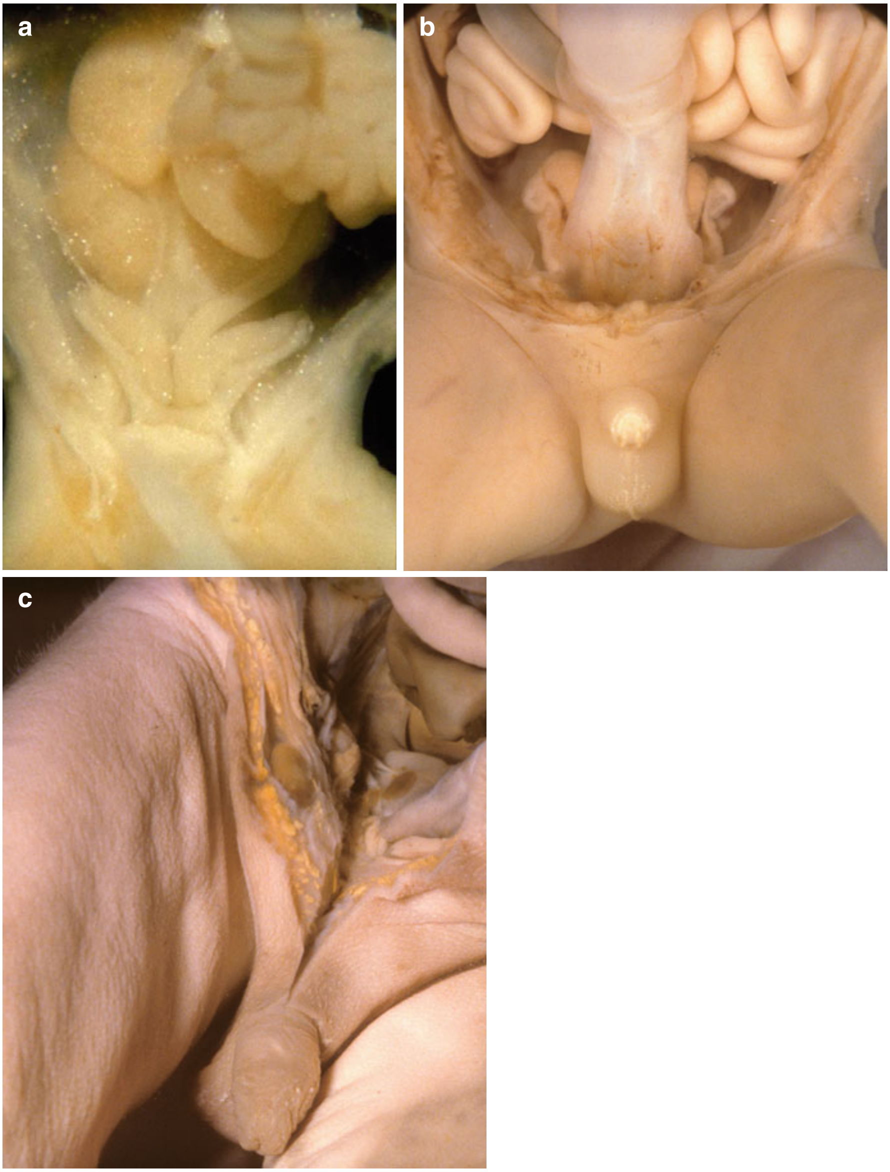


Fig. 2.4 (**a**) Human male fetus at week 8, showing the testis in the same position as the ovary in Fig. 2.3a. (**b**) Human male fetus at week 13, with the testes at the bladder neck and the swelling reaction in the gubernaculum partly obscured by the umbilical arteries. (**c**) Human male fetus at week 24, showing testis just inside the inguinal canal

fetal rat gubernaculum, but their maximum expression was between days 18 and 21, which is after the swelling reaction is almost complete in this animal, and after the 'fetal programming window' for androgen that has been identified recently [27]. Androgen receptors are found also in the gubernaculum of the fetal pig [28], but both the receptor binding affinity and its capacity are significantly lower than in

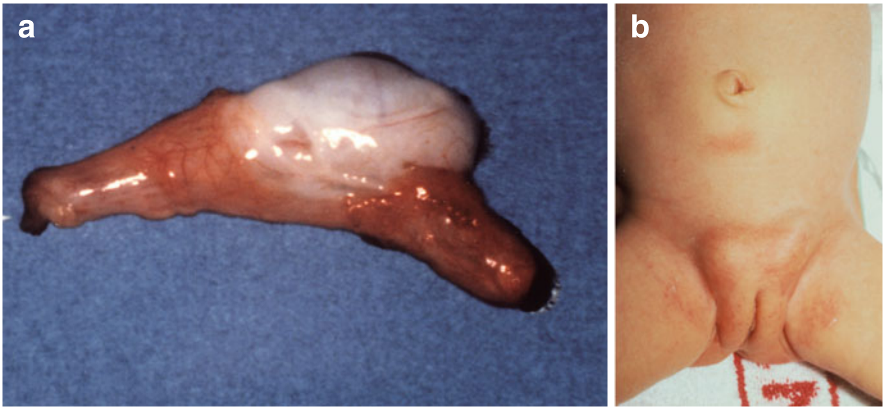


Fig. 2.5 (**a**) A testis and gubernaculum excised from a human with complete androgen resistance. Despite absence of androgen receptors (and hence no epididymal development), the gubernaculum has undergone a normal 'swelling reaction' Hutson et al. [49]. (**b**) One-week-old infant with 46, XY disorder of sex development (DSD), where there is complete androgen resistance and normal female phenotype. The transabdominal migration of the testes is normal, but inguinoscrotal migration is absent, leaving the testes in the groin (Reproduced with permission from Hutson et al. [50])

known androgen-sensitive target tissues (e.g. prostate). Spencer et al. [29] showed that the anti-androgen, flutamide, given between days 15 and 17 of gestation of a rat, could prevent testicular descent at 28 days after birth. There is some hypoplasia of the gubernacular swelling reaction (20 %), but the testes are nearly all descended through the inguinal canal, confirming that transabdominal descent is not interrupted significantly. These studies were interpreted as supporting a role for androgens in transabdominal descent, although in retrospect, they merely confirmed that transabdominal descent did not need androgen stimulation.

2.3 Insulin-Like Hormone 3 (INSL3)

In 1999, it was found in two independent laboratories that a low molecular weight substance produced by the Leydig cells, insulin-like hormone 3 (INSL3), caused cryptorchidism in mice with a targeted deletion of the gene [30, 31]. Similar to testosterone, INSL3 production is responsive to trophic stimulation by luteinising hormone (LH), but its production is less sensitive to LH levels than testosterone [32]. Acting through its receptor in the gubernaculum, relaxin family peptide receptor 2 (RXFP2), INSL3 stimulates the swelling reaction in the gubernaculum [33, 34].

INSL3 is synthesised in the fetal testis at the right time to initiate the swelling reaction of the gubernaculum, and in vitro studies confirm that it triggers gubernacular growth [35]. Both testosterone and AMH have some minor trophic effects on the rat gubernaculum in organ culture but are presumed to merely augment the effect of INSL3 [35]. (There is some indirect evidence, however, that AMH may have a role in controlling the length of the gubernacular cord (see below).)

INSL3 is a member of the insulin family of related hormones and growth factors. It is synthesised as a preprotein of 131 amino acids which contains a 24-amino acid signalling peptide. Transgenic overexpression in female mice of INSL3 leads to the swelling reaction occurring in the gubernaculum, which causes the ovaries to descend to the bladder neck in a similar way to transabdominal descent in males [36]. Recent studies demonstrate that INSL3 acts in the gubernacular cells via the NOTCH and Wnt/β-catenin pathways [32, 37–39].

Despite convincing evidence for INSL3 regulating the swelling reaction of the gubernaculum, INSL3 mutations or defects in its receptor are uncommonly found in cryptorchid children [32, 40] which may be related to the fact that intra-abdominal undescended testes are uncommon. Further genetic analysis may find defects in some of the 'downstream' intracellular signalling pathways, such as in the Wnt-5α/Ror2 pathway that has been identified as the cause of the rare Robinow syndrome [39, 41–44].

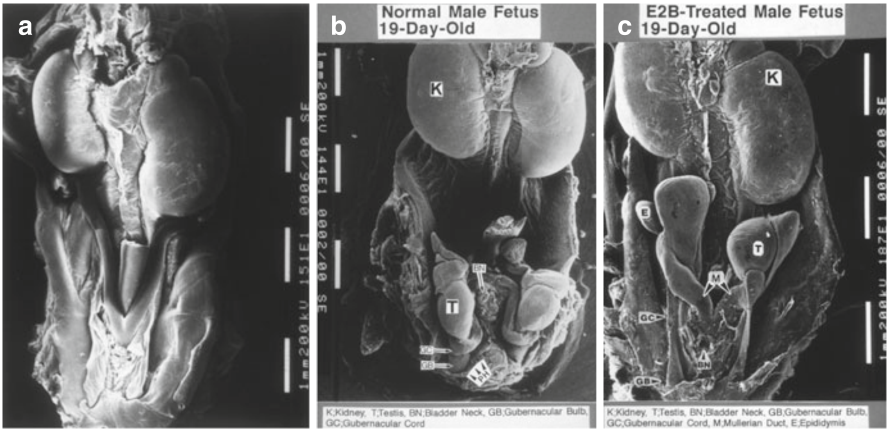
Identification of INSL3 has provided an explanation for how exogenous oestrogen causes cryptorchidism, as in utero oestrogen exposure inhibits Leydig cell function directly as well as indirectly by low LH concentrations [32, 45] (see below). Whether or not INSL3 has other functions aside from the gubernacular swelling reaction remains to be determined, although there is some indirect evidence that it may play a minor role in the inguinoscrotal phase of descent [46, 47].

2.4 Oestrogen-Treated Mouse

Fetal male mice exposed to exogenous oestrogen have undescended testes. This was initially interpreted as evidence for interference with androgen action [9], but since the discovery of INSL3, it is now recognised that oestrogen inhibits INSL3 as well as androgen. The degree of androgen suppression by INSL3 was directly related to the degree of atrophy of the Wolffian duct, consistent with simultaneous suppression of androgen-dependent development [48].

Oestrogen injected into pregnant dams completely blocks testicular descent in male offspring, with the testis located at the lower pole of the kidney (Fig. 2.6) [49, 50]. When human chorionic gonadotrophin is injected simultaneously with oestrogen, the circulating androgen levels are not inhibited as much as with oestrogen alone, but the testis remains completely undescended [49–51]. Secondly, when testicular feminising male (TFM) mice with complete androgen resistance are exposed to oestrogen in utero, they also demonstrate complete lack of descent of the testis, while in normal TFM mice or after flutamide treatment to block androgens, the testis is descended to a position beside the bladder neck by birth [7] (Fig. 2.7), consistent with oestrogen interfering with INSL3.

A striking feature of the fetal mouse exposed to oestrogen is the persistence of the Müllerian ducts in genetic males [8], suggesting that AMH may be involved. However, when pregnant mice were treated with oestrogen on day 15 of gestation, which is after regression of the Müllerian duct, the offspring still has UDT at birth, even though the Müllerian duct is represented by only a few vestigial cysts [52, 53]. This experiment showed that oestrogen blocked both testicular descent and Müllerian duct regression by suppression of both AMH and INSL3.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19-Day-Old
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c
E2B-Treated Male Fetus
19-Day-Old
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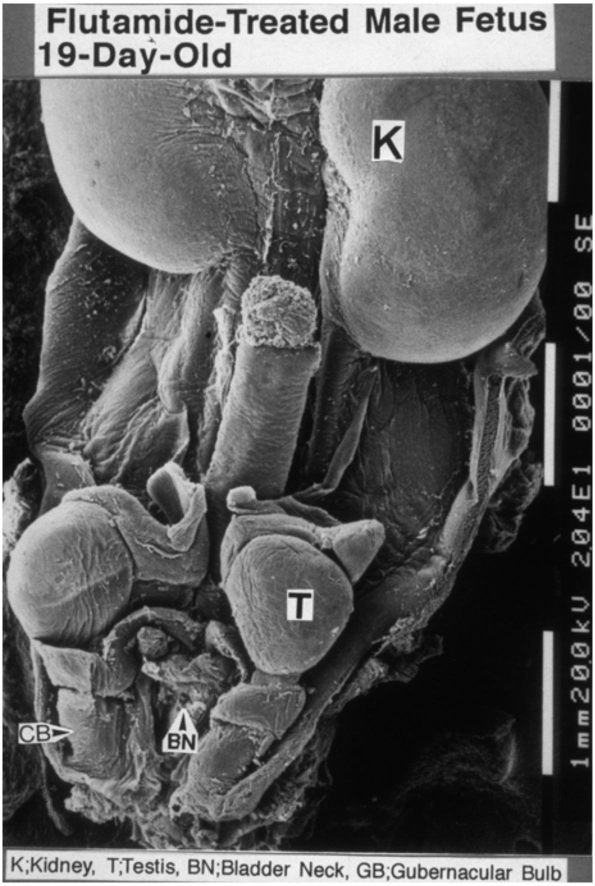
K;Kidney, T;Testis, BN;Bladder Neck, GB;Gubernacular Bulb, GC;Gubernacular Cord, M;Mullerian Duct, E;Epididymis

Fig. 2.6 (**a**) Scanning EM of neonatal female mouse showing ovaries adjacent to lower pole of kidneys and Müllerian ducts now developed into uterus of fallopian tubes. The gubernaculum is now a round ligament connecting the uterus to the inguinal abdominal wall. (**b**) Scanning EM of neonatal male mouse showing testes descended to the bladder neck and the swelling reaction in the gubernaculum. (**c**) Scanning EM of neonatal male mouse exposed to prenatal oestrogen showing persistence of the Müllerian ducts as primitive uterus and tubes and lack of testicular descent caused by absence of the swelling reaction in the gubernaculum, which has the appearance of a female round ligament (Reproduced from Shono et al. [15])

2.5 Persistent Müllerian Duct Syndrome

Although INSL3 is the hormone controlling the swelling reaction in rodents, in humans AMH may have a supplementary role in preventing elongation of the gubernacular cord (i.e. that part of the gubernaculum that attaches to the testis and epididymis), as seen in the rare clinical disorder of persistent Müllerian duct syndrome. This is a genetic abnormality of AMH secretion or its receptor. Affected patients have normal male external genitalia but completely retained Müllerian ducts (fallopian tubes, uterus, and upper vagina) as well as UDT [53–56]. The female genital tract structures are small because of the absence of oestrogen in the male. Most boys with this abnormality have testes in a pseudoovarian position (Fig. 2.8) [57], which has also been reported in the bull [58]. The gubernacular cord in this syndrome is abnormally long, which may predispose to the rare abnormality of transverse testicular ectopia, which is present in 10 % of these patients [7, 59]. In this variant both testes are in the same inguinal hernial sac, and each testis is connected to its ipsilateral inguinal ring by an extremely elongated gubernacular cord (over 10 cm in length) (Fig. 2.9).


Flutamide-Treated Male Fetus
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T
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K;Kidney, T;Testis, BN;Bladder Neck, GB;Gubernacular Bulb

Fig. 2.7 Scanning EM neonatal male mouse treated prenatally with the anti-androgen, flutamide, showing undescended testes and absence of the swelling reaction in the gubernaculum (Reproduced with permission from Shono et al. [15])

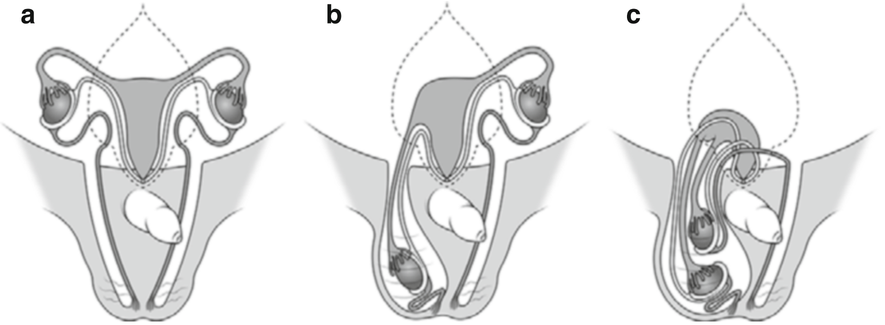

Fig. 2.8 The three clinical presentations of persistent Müllerian duct syndrome: (**a**) the majority (60–70 %) of patients have testes in the normal position of ovaries, and the inguinal hernial sacs remain empty. (**b**) A smaller group (20–30 %) have one testis in an inguinal hernia or the scrotum along with its attached tube and uterus. This is known as 'hernia uteri inguinalis'. (**c**) About 10 % of patients have both testes herniated into one processus vaginalis (transverse testicular ectopia)

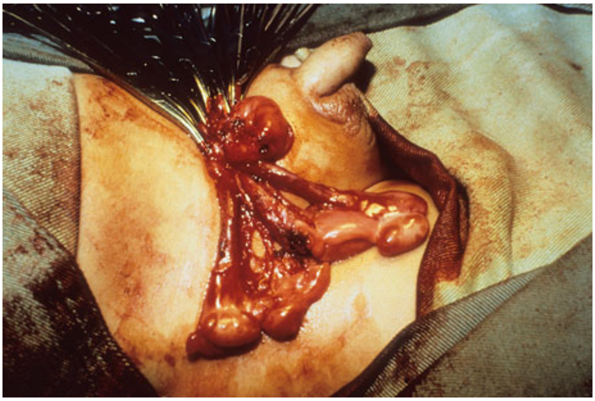

Fig. 2.9 A boy with persistent Müllerian duct syndrome and transverse testicular ectopia. Operative photograph showing both testes and the uterus and tubes in a right inguinal hernia. Note the lack of gubernacular attachments (Reproduced with permission from Hutson et al. 1987)

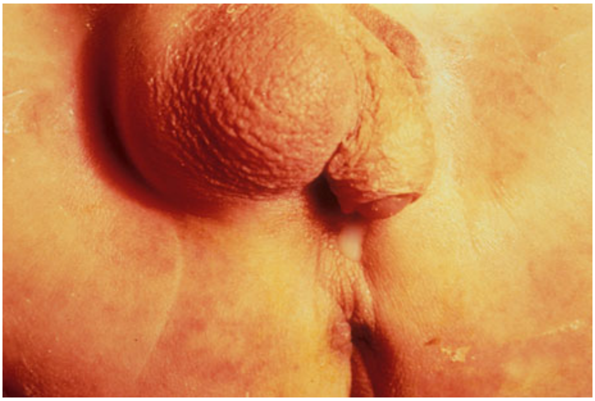

Fig. 2.10 The external genitalia of a patient with mixed chromosome DSD with gonadal dysplasia (mixed gonadal dysgenesis). On the right side the gonadal development is less affected, with some local secretion of testosterone and AMH: the testis has descended and the ipsilateral Müllerian duct has regressed. The left gonad is completely dysplastic ('streak' gonad) and has failed to descend at all. The adjacent Müllerian duct is retained. Note the vaginal mucus (stimulated by maternal hormones) at the opening of the urogenital sinus

The strong association in this syndrome between the degree of Müllerian duct regression and the degree of gubernacular development and testicular descent is seen also in other types of disorders of sex development (DSD) from other causes where the testis is dysplastic (Fig. 2.10), where the degree of Müllerian duct retention is directly related to the degree of gonadal descent [60, 61]. The link between Müllerian duct regression and transabdominal testicular descent in the human suggests that AMH may be augmenting the effect of INSL3 on the swelling reaction by controlling the length of the gubernacular cord which attaches the testis and epididymis to the gubernacular bulb. However, AMH is not primarily responsible for the swelling reaction itself [62].

Conclusion

Transabdominal movement of the testis towards the future inguinal canal is mostly relative to other structures, which are moving away from the groin as the fetus enlarges. The testis is held close to the inguinal region by a 'swelling reaction' in the gubernaculum which is controlled by INSL3. In rodent models, the gubernacular cord stays quite long, while in humans it remains short, and this shortening may be regulated by AMH, as in humans with defects in AMH signalling, they have an extremely long gubernacular cord.

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Inguinoscrotal Descent of the Testis

3

3.1 Migration of the Gubernaculum

The inguinoscrotal phase of testicular descent begins at about 25 weeks' gestation in the human fetus [1, 2]. Between weeks 26 and 28, the testis descends rapidly through the inguinal canal and then moves more slowly towards the scrotum, reaching it at 35–40 weeks [2]. In the human, migration of the gubernaculum and the testis occurs simultaneously (Figs. 3.1 and 3.2) [3, 4], while in rodents, migration of the gubernaculum precedes testicular descent [5, 6] as the gubernacular cord is longer. In rats, the gubernaculum migrates postnatally from the inguinal region to the scrotum between 3 and 10 days of age, and in the mouse this occurs by about 1 week [7]. Migration of the testis itself in rodents is delayed until the onset of pubertal hormone stimulation, which in the mouse occurs at about 2–3 weeks and in the rat at 3–4 weeks. Prior to the inguinoscrotal phase of migration, in both humans and rodents, the gubernaculum ends at the abdominal wall, as shown a century ago by Cleland [8] and more recently by Fallat in rodents and Barteczko and Jacob and Heyns in the human [3, 7, 9] and demonstrated in Figs. 3.1 and 3.2.

The processus vaginalis initially forms as a small evagination of the peritoneum into the gubernacular mesenchyme at the site of the future internal inguinal ring (Fig. 3.3) [1]. This peritoneal diverticulum later elongates within the gubernaculum to form an annular cavity, dividing the gubernaculum into a central mesenchymal column and an outer parietal layer. Following complete descent of the testis in a boy, the central gubernacular column involutes by dissolution of the extracellular matrix. The residual tissue of the column forms the fibrous attachment of the testis to the scrotum.

The cremaster muscle develops within the outer parietal layer of the gubernaculum, forming a bilaminar sac in rodents and a strip of muscle in ungulates and primates [10, 11]. The attachment of the cremaster muscle to the inguinal abdominal

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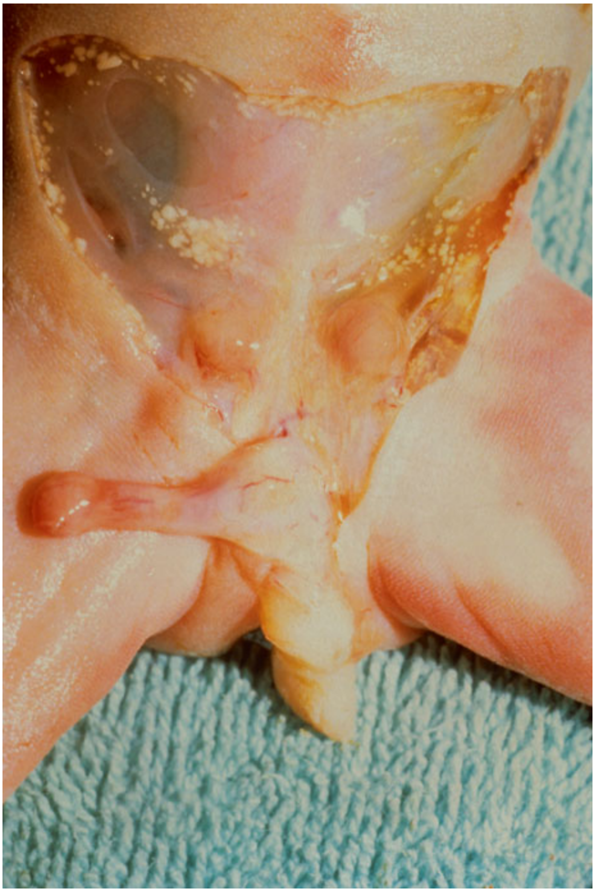

Fig. 3.1 Dissection of a 30-week human fetus showing gubernaculum emerging from the external ring (Reproduced with permission of the publisher from Heyns [9])

wall varies from species to species [6], but in all mammals, it is supplied by its own nerve: the genital branch of the genitofemoral nerve [3, 12, 13].

During gubernacular migration, its distal migrating edge in the human is ovoid or spherical, while in the rodent it is conical. Careful dissection of the distal end of the gubernaculum in humans (Fig. 3.2) [2], pigs [1], and rodents [7] shows that during inguinoscrotal descent, the lower end of the gubernaculum is free and unattached to the adjacent mesenchyme. This has been used as evidence against the concept of the gubernaculum pulling the testis down to the scrotum, since it is not anchored inferiorly [1, 9, 14]. It is now appreciated, however, that the gubernaculum is migrating towards the scrotum by clearing the space ahead of it by enzymatic digestion (Fig. 3.3). A potentially fruitful area of research, therefore, will be histochemical analysis of this region looking for evidence of enzymatic activity [15].

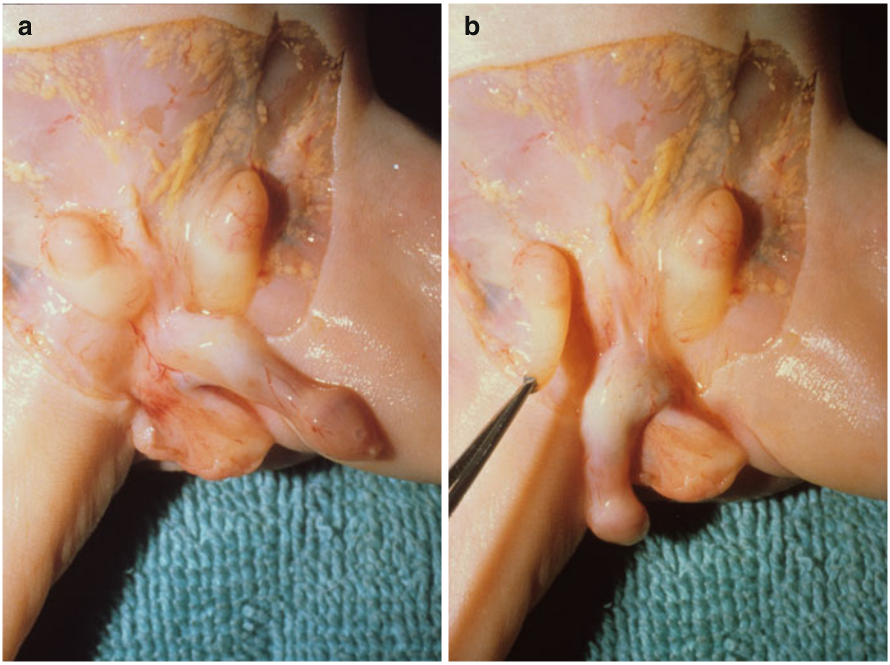

Fig. 3.2 (**a**) Dissection of a 32-week human fetus showing the gubernaculum and testis migrating across the pubic region towards the scrotum. (**b**) A pair of forceps holds up the free caudal end of the gubernaculum (Reproduced with permission of the publisher from Heyns [9])

3.2 Intra-abdominal Pressure

The force required to assist elongation of the processus vaginalis may be intra-abdominal pressure: this has long been assumed to push the testis down the inguinal canal [16]. Studies on rats also suggested an important role for abdominal pressure [17–20]. This possibility is supported by the fact that male human infants with severe abdominal wall defects, where abdominal pressure may be lower than normal, have a high incidence of undescended testes (UDT) [21] (see Chap. 5).

3.3 The Role of Testosterone

Studies in rodents demonstrated an important role for androgens in inguinoscrotal descent [22–25]. For example, androgen treatment or gonadotrophin treatment in immature rats causes premature testicular descent [22]. This effect of androgen treatment in prepubertal animals may be misleading, however, since Backhouse [1] suggested that the important anatomical developments had been completed shortly after birth in the rodent and that subsequent hormonal treatment essentially was stimulating precocious puberty. Similarly in the macaque, postnatal administration

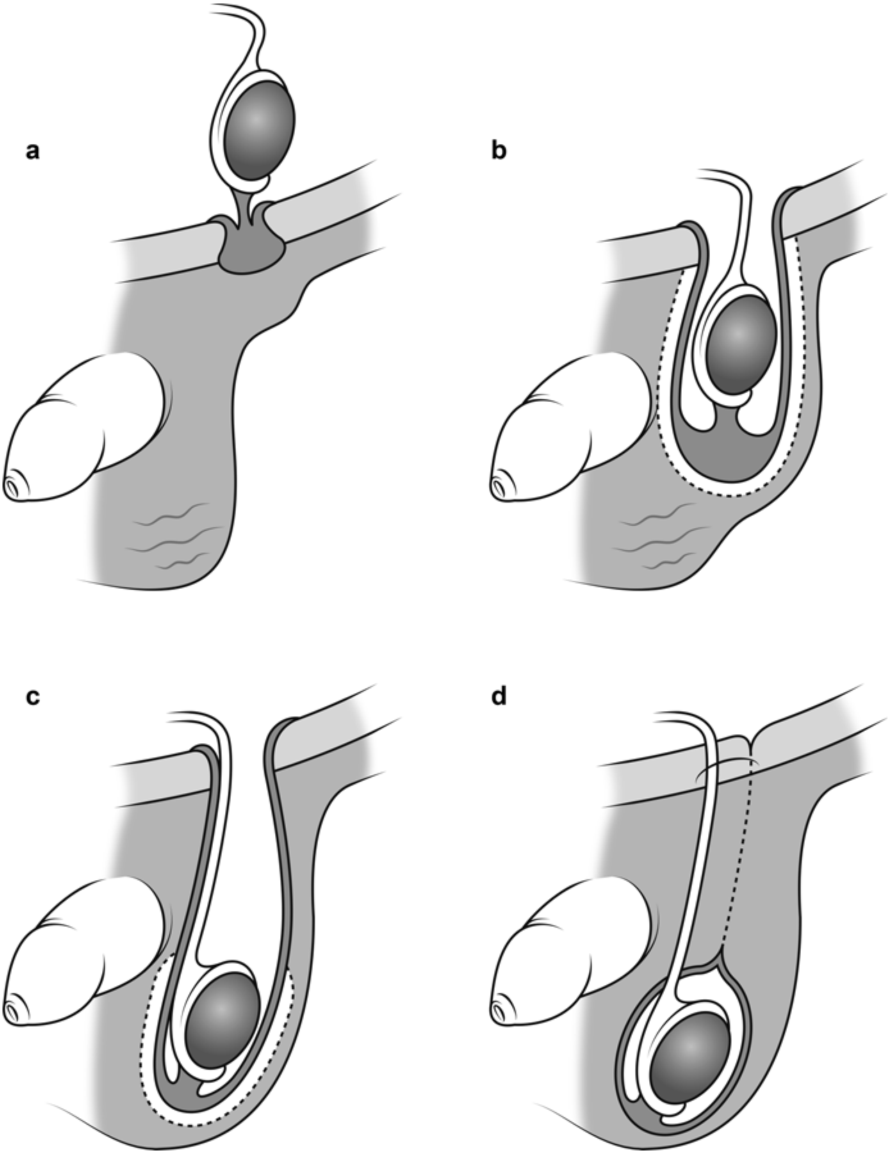

Fig. 3.3 Diagram of the gubernaculum with its developing processus vaginalis prior to inguinoscrotal descent. (**a**) Gubernaculum in abdominal wall after swelling reaction and before inguinoscrotal phase. (**b**) The gubernaculum migrating to the scrotum with testis inside it in the processus vaginalis. There is an enzymatically generated plane of cleavage around the gubernaculum. (**c**) The gubernaculum has arrived in the scrotum but is not yet fixed, potentially enabling perinatal torsion. (**d**) The last two steps in the process of testicular descent in the human have occurred: obliteration of proximal processus vaginalis and fibrous adherence of regressed gubernaculum to inside of the scrotum

of androgens induced precocious puberty, and the testis, which had reached the scrotum before birth and then ascended back to the groin in infancy, redescended to the scrotum [26]. Nevertheless, the failure of gubernacular migration and descent of the testis beyond the inguinal region in animals with complete androgen insensitivity demonstrated conclusively that androgens were crucial for this phase of descent. Even in the human with complete androgen insensitivity syndrome (CAIS), the testis never descended beyond the inguinal region [27] (see Fig. 2.3b). Also, in the rare genetic disorders of hypothalamic dysfunction, inguinoscrotal descent is deficient [28–31], and the length of the anogenital distance, which is regulated by androgen, correlates with testicular descent [32].

All these studies confirmed that androgens are important for inguinoscrotal descent, which is controlled by gubernacular migration. The gubernaculum was believed to be the direct target organ for androgens, but this has not been proven by the presence of androgen receptors within the gubernaculum [23, 33]. When Heyns and Pape [34] looked carefully at androgen binding in the fetal pig gubernaculum, they found both the receptor binding affinity and capacity were significantly lower than that of typical androgenic target tissues, such as the prostate and urethra.

Most importantly, in the detailed study in the rat, it was found that the effects of androgen were mediated by a narrow time window, between days 15 and 19 in the fetal rat [35], which is before the migration of the gubernaculum after birth.

Androgen receptors have been localised within the mesenchymal core of the fetal rat gubernaculum, but the level of their expression was low during the short programming window [36]. It is thought that testosterone controls masculinisation during a similar programming window in the human fetus at 8–14 weeks' gestation.

Knowing that testosterone acts in narrow time window in the fetal rat, we looked at AR in the gubernaculum and the dorsal root ganglion of the genitofemoral nerve (GFN) (see below). Surprisingly, AR were not present in significant numbers in the fetal rat gubernaculum until E19, just at the end of the programming window [37]. Moreover, they are also absent from the sensory cell bodies of the GFN in the dorsal root ganglion during the programming window [37]. By contrast, there were abundant AR in the inguinoscrotal fat pad just outside the abdominal wall, which is adjacent to the end of the gubernaculum prior to inguinoscrotal descent and a target organ for GFN sensory fibres [37, 38] (Fig. 3.4).

The anti-androgen, flutamide, causes inhibition of inguinoscrotal descent in rats but only when the compound is given between 12 and 18 days of gestation (i.e. during the programming window) and not when inguinoscrotal descent actually occurs, at 3–28 days after birth [39]. Although administration of oestrogens postnatally can prevent testicular descent at puberty [40], postnatal anti-androgens had no effect at all. This apparently paradoxical response to anti-androgens can be understood once the role of the genitofemoral nerve is appreciated, as described below, as androgens act on the inguinoscrotal fat pad to modify the GFN, which then controls migration of the gubernaculum in the first week after birth. Oestrogen administration is believed to inhibit subsequent pubertal development of the testis, such that it remains very small and never descends. Since the normal migration of the gubernaculum

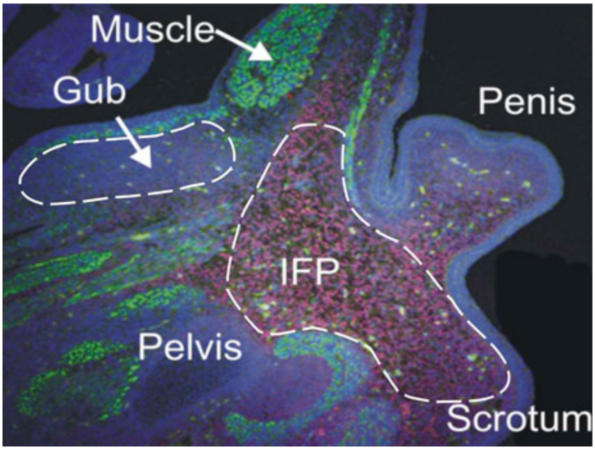

Fig. 3.4 Sagittal section of fetal rat (embryonic day 17) during programming window for androgen (E 15.5-E19.5). Androgen receptors (in *red*) are located throughout the inguinal fat pad (IFP) from the inguinal canal to the scrotum. By contrast, the gubernaculum (Gub), which initially ends in the inguinal muscles, contains no androgen receptors (Reproduced with permission from Allnutt et al. [38])

beyond the groin is absent in androgen-resistant mice [41], this process is definitely androgen-dependent, but cannot be inhibited by simultaneous androgen blockade.

When the anti-androgen, flutamide, is given to fetal rats during the programming window, it prevents inguinoscrotal descent and also causes persistence of the inguinal mammary buds which are immediately superficial to the end of the gubernaculum as the future external inguinal ring [42]. We found this anatomical relationship intriguing as it recreated what is normal in marsupials, where the GFN supplies the breasts in the groin and the homologue of the cremaster muscle, the ilio-marsupialis, which is the suspensory muscle of the breasts [43]. In addition, the fact that in ungulates the breasts (the udder) and the scrotum are in the same location is consistent with a common embryological origin (see Fig. 1.11).

It is likely that signalling from the inguinal fat pad along the mammary line triggers the underlying gubernaculum to begin migrating to the scrotum [44] like a limb bud [45–47] (Fig. 3.5).

The mammary line is derived from the skin at the junction of the dorsal and ventral surfaces of the early mammalian embryo and carries the same genetic programming as the upper and lower limb buds, which arise at the cranial and caudal ends of the mammary line [48]. With three-dimensional folding of the embryo, the mammary lie comes to line between the anterior axillary fold, through the normal site of the breasts in humans and down to the future inguinal canal, and ending in the medial upper thigh. This specialised skin has the ability to induce the underlying tissue to sprout, so that initial protrusion of the gubernaculum beyond the inguinal muscles at the future external inguinal ring is likely to be very similar to an embryonic limb bud [49, 50]. It is not surprising, therefore, that the rodent gubernaculum elongates by growing from its tip, just like a limb bud [46, 51–53]. The homeobox

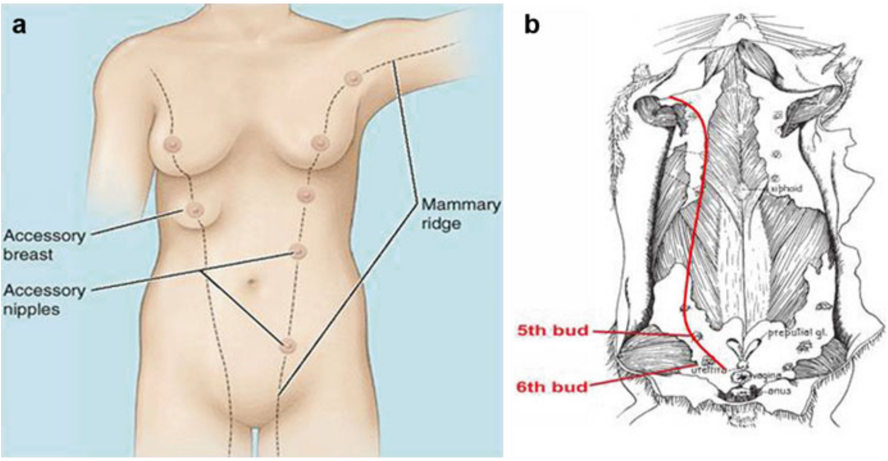

Fig. 3.5 The developmental mammary line in humans and rodents. (**a**) Mammary line in the human. Polymastia and polythelia can occur anywhere along this line. (**b**) Rat mammary line and mammary fat pads. The sixth mammary bud is directly over the inguinal canal during embryonic development

gene Hoxa11, which is involved in patterning embryonic structures, is necessary for gubernacular development and may be regulating the growth centre in the tip of the gubernaculum during migration [54–56].

3.4 The Genitofemoral Nerve (GFN) Hypothesis

In 1948, Lewis [57] attempted to show that cremasteric contraction was the active step in testicular descent. He reasoned that since the genitofemoral nerve (GFN) supplied the cremaster muscle, transection of the nerve would paralyse the muscle and prevent descent. He transected the GFN in newborn rats and found that this prevented testicular descent, apparently supporting his hypothesis for cremasteric contraction. Many workers were critical of his experiment and conclusions, however, because they believed that contraction of the cremaster would pull the testis up to the groin, rather than down to the scrotum.

Years ago we repeated this experiment and likewise found that transection of the GFN prevents inguinoscrotal descent of the testis in the neonatal rat [58]. In rats where the GFN was divided successfully at birth, the ipsilateral testis remained intra-abdominal. The effect of nerve transection was greatest in the first 2 days after birth, and thereafter there was a diminished effect on gubernacular migration. After 4 days, there was no effect at all. These studies suggested a crucial role for the GFN in gubernacular migration. At first, there was no explanation as to why nerve transection caused the gubernaculum to lose its apparent sensitivity to hormone stimulation. The need for an intact nerve supply did not concur with other endocrinological systems, where target organs remain sensitive to their specific hormone despite complete denervation or even transplantation. To overcome this difficulty, we proposed the simple hypothesis that the testosterone may act primarily on the GFN, rather than directly on the gubernaculum. The GFN could then act as an effective 'second messenger' for androgenic stimulation of the gubernaculum [58].

Initial support for the role of the GFN in gubernacular migration was seen in children with spina bifida, particularly where the myelomeningocele was in the high lumbar region, the origin of the GFN [59]. Spinal cord transection in neonatal rats caused undescended testis when it was performed in the low thoracic or high lumbar region [59].

3.5 Sexual Dimorphism of Genitofemoral Nerve

For the GFN to mediate androgen, it must undergo sexual dimorphism, i.e. it should be structurally modified by androgens in the male. We searched for a specific neuropeptide neurotransmitter within the genitofemoral nerve in the male [60] that might function as a hormone. We tested a number of neuropeptide neurotransmitters with immunohistochemistry on the GFN motor nucleus and identified that calcitonin gene-related peptide (CGRP) was found in the same area. Further study of the GFN motor nucleus, however, showed CGRP was downregulated in the male, so we went back and did a more detailed study and found that CGRP was present in the male GFN but actually was in the sensory fibres, not in the motor nerves [61–63].

In a related study, we found that the GFN had presumed sensory branches containing CGRP which supplied the inguinoscrotal fat pad ahead of the migrating gubernaculum [64]. The unique position of the GFN in the scrotal region [3] and its sexually dimorphic neurotransmitter CGRP were consistent with the hypothesis that in response to androgen the nerve may release CGRP as a chemotactic regulator of the gubernaculum in its migration. In a study of human fetuses, Barteczko and Jacob [3] found that the GFN was closely associated with the gubernaculum, and its terminal sensory branches preceded the gubernaculum to the scrotum, consistent with the nerve providing a directional signal for gubernacular migration. Our recent work suggests that the nerve may be modified by neurotrophin released in the inguinal fat pad in response to androgen signalling (Fig. 3.6).

3.6 The Effect of CGRP

When neonatal rat gubernacula were placed in organ culture and various concentrations of CGRP were added, to our great surprise we found that CGRP induced rhythmic contractions of the gubernacular cremaster muscle at rates of up to 250 contractions per minute (Fig. 3.7) [65]. This remarkable observation totally changed our view of the gubernaculum. Prior to this observation, it was imagined that the gubernaculum was relatively inert mesenchyme (that could respond to insulin-like hormone 3 (INSL3) by enlargement). Now we appreciate that the gubernaculum becomes an actively contractile and motile structure during inguinoscrotal migration.

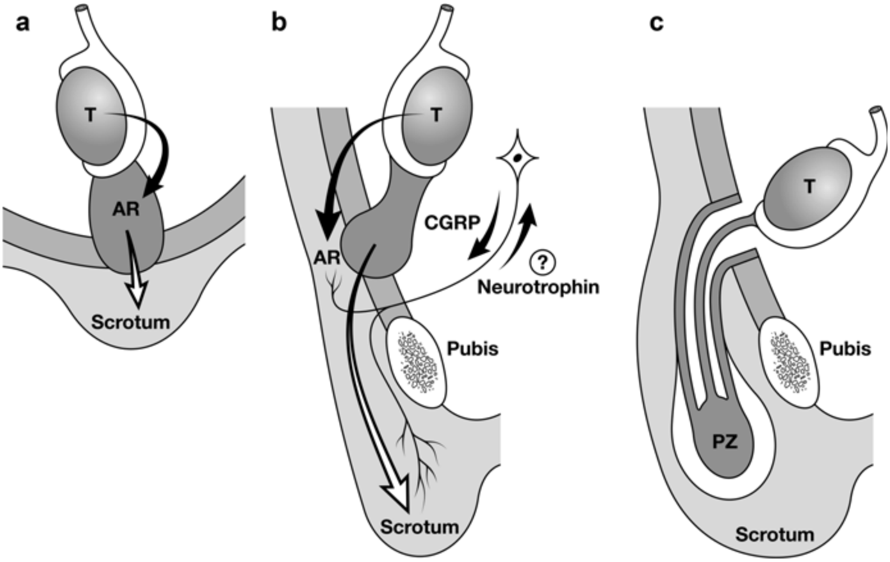

Fig. 3.6 Our current hypothesis about how androgens act mostly indirectly on the gubernaculum via the GFN and its neurotransmitter, CGRP. (**a**) The original hypothesis suggested testosterone from the testis (*T*) acted on the AR of the gubernaculum to trigger it to simply bulge into the apparently adjacent scrotum. (**b**) Our current hypothesis shows testosterone from the testis (*T*) acts on the AR in the subcutaneous mesenchyme of the mammary line, immediately superficial to the gubernaculum, which ends in the inguinal abdominal wall muscles. AR stimulation of the mesenchyme is proposed to cause production of a neurotrophin, which is taken up by the GFN sensory fibres and masculinises the nerve. The GFN then produces CGRP, which is released from the sensory nerve endings to guide the migration of the gubernaculum to the scrotum, which is in the perineum. (**c**) During inguinoscrotal migration, the PV hollows out the gubernaculum, which remains attached to the testis (*T*) and epididymis by the gubernacular cord. The distal, solid tip of the rodent gubernaculum contains undifferentiated mesenchyme, which has properties similar to a 'progress zone' (*PZ*) in an embryonic limb bud. Enzymes dissolve the extracellular matrix so that the tip of the gubernaculum is loose under the skin during migration

Similar studies were performed using the neonatal mouse gubernaculum in organ culture. About half the gubernacula placed in culture showed endogenous contraction, and this increased in a dose-responsive manner when exogenous CGRP was added to the medium [66]. When a synthetic antagonist of CGRP was added to the culture system, contractions were inhibited in a dose responsive way (CGRP8-37 is an analogue of CGRP that binds to the receptor but has no function). Furthermore, the neonatal mouse gubernaculum with complete androgen insensitivity [64] showed no endogenous contraction at all but when CGRP was added to the medium, the gubernacula responded with greatly enhanced contractions, consistent with hypersensitivity to CGRP [66] when androgen signalling is blocked.

Examination of the gubernaculum in situ in neonatal rats under anaesthesia showed a conical structure emerging from the inguinal canal. The caudal end of the gubernaculum was not attached to surrounding subcutaneous tissues, and this leading edge twitched and was contractile. When the abdominal pressure was increased

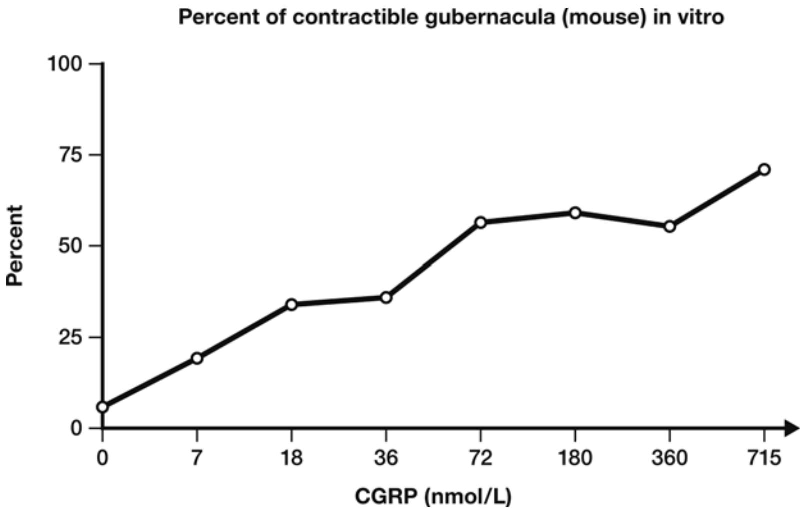

Fig. 3.7 Number of contractile gubernacula at different concentrations of CGRP ($n=206$). The number on each column indicates the percentage of contractile gubernacula (Reproduced with permission of the publisher from Park and Hutson [65])

by manual compression, increasing the pressure within the processus vaginalis, the contractility of the gubernaculum became more vigorous [65]. The appearance of the gubernaculum was reminiscent of a windsock on a windy day.

Confirmation that CGRP had specific effects on the gubernaculum and direct involvement in testicular descent was provided by the demonstration of specific binding sites for CGRP by autoradiography of neonatal rat gubernacula [67, 68]. In a related experiment, injection into neonatal mice of CGRP 8-37, an antagonist of CGRP, caused a delay in testicular descent—from the normal 2 weeks to 4 weeks, postnatally [69]. CGRP acts via cyclic AMP [70], and the response of the gubernaculum is controlled by androgen exposure: in the AR blockade mouse (TFM), the AR are upregulated in the gubernaculum [71] similar to flutamide exposure [72], while the sensory nerve toxin blocks CGRP effects [73, 74]. CGRP stimulates cell division in the growing tip of the gubernaculum [75], but AR are necessary in the gubernaculum for this response [76], and the main role of CGRP may be to provide a chemotactic signal to direct migration to the scrotum [53]. A distal growth centre in the gubernaculum which responds to CGRP has properties very similar to that in an embryonic limb bud [46].

3.7 The GFN in Humans Versus Rodents

The role of the GFN in testicular descent in rodent models is now well established, but there are still some important unanswered questions. Before we knew that there was a short ‘programming window’ for androgens, it was assumed that the AR were just in the gubernaculum itself [36]. Recognition of the presence of AR in the inguinoscrotal fat pad at the right time along the mammary line provided a theoretical explanation of how the gubernaculum could be controlled indirectly by androgens. However, the inguinoscrotal fat pad would have to produce a neurotrophin to 'masculinise' the sensory branches of the GFN, similar to how the bulbocavernosus muscle masculinises the pudendal nerve [77]. Our recent results suggest that the fat pad may also produce brain-derived neurotrophin factor (BDNF) and ciliary neurotrophic factor (CNTF) like the bulbocavernosus muscle (unpublished). After the programming window, the gubernaculum itself acquires AR that are required for the responses by the gubernaculum to CGRP from the GFN [76].

Even accepting the fact that the GFN in rodents may be masculinised by peripheral neurotrophins synthesised by the target organ, many investigators remain sceptical about a role for the GFN in humans [78]. Clearly there are some major anatomical differences between rodents and humans, as the processus vaginalis (PV) obliterates after testicular descent in humans, while in rodents it remains patent through life [79], so that in the adult rat, the testis can retract back into the peritoneal cavity, where it can be seen to be on a mesentery (Fig. 3.8). The species differences in the PV stimulated us to consider the role of the PV more formally.

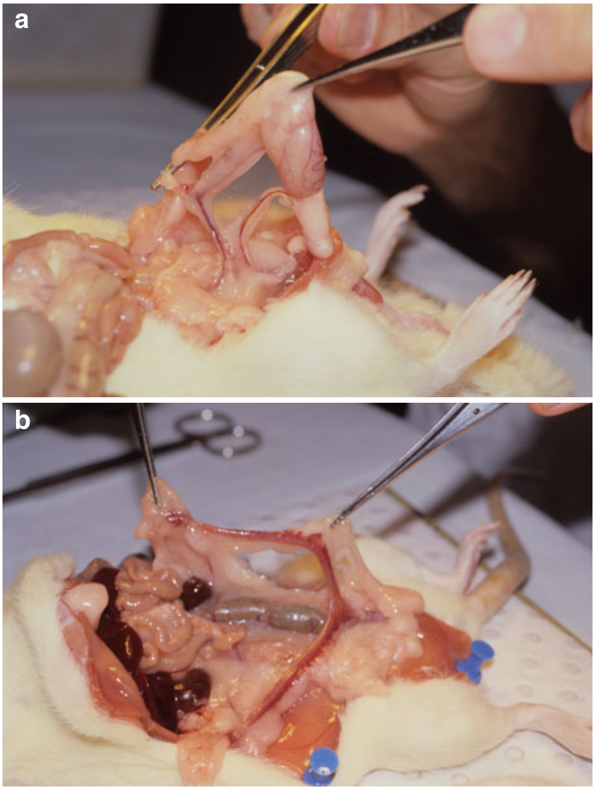

Fig. 3.8 Photographs of the internal genital anatomy in an adult Sprague-Dawley rat, showing (**a**) the male and (**b**) the female. In both genders, the gonad and genital ducts are in a fold of the peritoneum. In the male, the testis has been pulled back through the patent inguinal canal to show the mesorchium and the gubernacular cord (Reproduced with permission from Miller et al. [83])

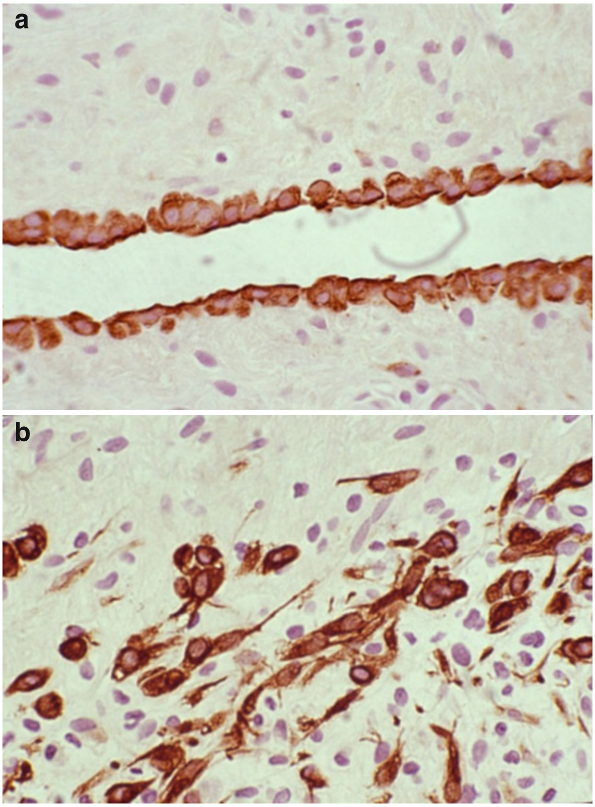

Fig. 3.9 Human PV that has been excised during an inguinal herniotomy and then placed in organ culture for 48 h. The peritoneal epithelial cells are labelled with cytokeratin. (**a**) Culture without exogenous CGRP. (**b**) Culture with CGRP, showing obliteration of the lumen as the epithelial cells transform into motile mesenchymal cells (Reproduced with permission from Hutson et al. [80])

As the intra-abdominal fetal testis needs the PV to develop inside the gubernaculum for descent to occur beyond the abdominal wall, we wondered whether subsequent PV closure in boys after descent might be controlled by the same mechanism that controls descent itself. We hypothesised that PV closure may be the ‘last step’ of testicular descent in humans and, if so, should be controlled by the GFN (and CGRP) if the latter is important in humans. When we tested this experimentally, we immediately found that exogenous CGRP triggered PV obliteration of inguinal hernia in vitro [80] (Fig. 3.9).

Conclusion

Our work on the inguinoscrotal migration phase of the gubernaculum and testis has shown an important role for the GFN in the rodent model. Whether this is directly applicable to the human is hard to test, but the patent processus vaginalis (PV) in children with inguinal hernia contains CGRP nerves [81] and the PV obliterates in vitro with exogenous CGRP [80, 82]. As closure of the patent PV in humans is the putative last step of testicular descent, it is likely that inguinoscrotal migration of the gubernaculum is controlled by the GFN and CGRP release from its sensory fibres similarly to that found in rodent models.

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Classification and Causes of Undescended Testes in Humans

4

4.1 Classification of Undescended Testes

For the purposes of understanding the pathogenic factors related to the different types of undescended testes (UDT) and evaluation of clinical results after treatment, a classification system is necessary. However, in the literature there is no consensus on definitions and terminology. The clearest classification system divides UDT into unilateral or bilateral cases and palpable and nonpalpable groups [1, 2]. However, for studies on the aetiology and epidemiology of UDT and in order to compare treatment studies, a classification system should describe the testicular position (Fig. 4.1a, b) [2, 3]. It has to be recognised though that the testis is not an immobile or fixed structure with a single location; instead, it has often a 'range of movement' [4]. This movement may be a result of the cremasteric reflex and contraction of the dartos muscle and is a normal finding in all prepubertal boys. Movement of the testis is also possible by virtue of its position within the processus vaginalis (PV), particularly when it is in the superficial inguinal pouch at the level of the external inguinal ring (Fig. 4.1a): its loose attachments via the mesorchium enable the testis to move anywhere within the PV.

Terms such as UDT, retentio testis, cryptorchidism, and maldescended testis all describe a testis that is not normally located at the bottom of the scrotum. An UDT is one which cannot be manipulated to the bottom of the scrotum without undue tension on the spermatic cord (see Chap. 7). The corollary of this is that a descended testis is one which can reside in the lower scrotum, irrespective of its position at the time it is first located. The various terms which are used to describe the location of a testis which cannot be made to reach the bottom of the scrotum are discussed below.

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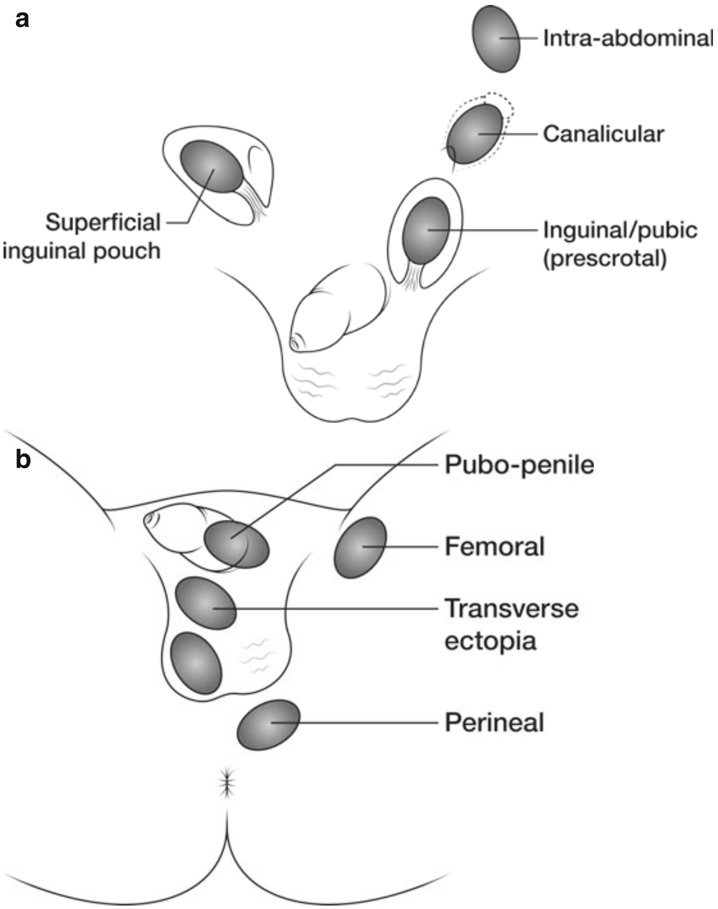

Fig. 4.1 Range of positions which may be adopted by the testes: (**a**) in the line of normal descent (including the superficial inguinal pouch) and (**b**) true ectopic sites, which are rare

4.1.1 Intra-abdominal Testis

When the testis is located in the abdominal cavity, it is impalpable clinically, and the position should be documented by laparoscopy (Chap. 7). Reported results show that about 5 % of operated UDT are intra-abdominal [5–7]. The intra-abdominal testes are further classified as closed-ring and open-ring variants, depending on the status of the internal ring of the inguinal canal [5–9].

If on laparoscopy vessels are not seen exiting the internal ring and the testis is found in an intra-abdominal position, there are several possibilities. Approximately half of the intra-abdominal testes are located close to the internal ring and are described as low 'intra-abdominal' (32–57 %) (Fig. 4.2). This group may include a variant called the 'peeping testis' in a position just at the internal ring, which are specified to constitute between 16 % and 39 % [10–12] of the total number of

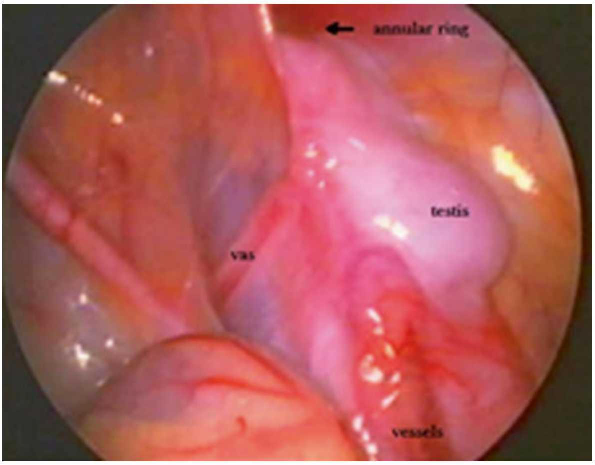

Fig. 4.2 Intra-abdominal testis located close to the internal ring identified by laparoscopy. Note the gubernaculum entering the open internal annular ring

intra-abdominal testes. Then, 42–61 % of the intra-abdominal testes are located at the iliac vessels or higher and are not related to the internal ring (high intra-abdominal) – in some studies at a distance greater than 2 cm to the internal ring [10–13]. Other positions include sub- or pararenal (which is reminiscent of the normal position of the ovary in many mammals, such as rodents), retrovesical, medial to the iliac vessels, or pararectal which together form less than 10 % [10, 12–14]. Bilateral intra-abdominal testes are seen in 14–25 % of the series with intra-abdominal testes [10, 15]. In 18–27 % of patients with intra-abdominal testes, associated abnormalities often related to the urinary tract or midline developmental field are found, especially in those with bilateral intra-abdominal testes [10, 15]). In order to introduce operative techniques, some authors have described the testicular blood supply to the intra-abdominal testis alternative to the testicular vessels [16–18]. But the variability is significant according to the position of the testis, and detailed systematic descriptions of the different types are still lacking. Often a good alternative blood supply is present in the gubernaculum or close to the vas (cremasteric artery and artery of the vas, respectively). But especially the subrenal testis or those far medial to the iliac vessels or in a retrovesical position may have a very sparse gubernaculum, and the viability is then dependent on the testicular vessels.

4.1.2 Canalicular Testis

A canalicular testis lies within the inguinal canal and is protected anteriorly by the aponeurosis of the external oblique muscle. The aponeurosis makes a canalicular testis difficult or impossible to palpate unless it can be coerced distally within its processus vaginalis through the external inguinal ring; in this situation, it is described as being an ‘emergent testis’, referring to the fact that it has been made to emerge from the inguinal canal.

4.1.3 Testis at the Level of External Annular Ring of the Inguinal Canal

This group of UDT includes those in the superficial inguinal pouch. This is a somewhat confusing term which has been used to denote the PV and its contained testis which has descended through the external ring to lie lateral or supero-lateral to the external inguinal ring (Fig. 4.1a). The testis has a longer spermatic cord than its intra-abdominal or canalicular counterpart and at orchidopexy requires relatively less mobilisation of the cord to achieve a satisfactory position in the scrotum. These UDT are prevented from entering the scrotum by a fascial barrier which can be felt at operation. Because the PV does not extend into the scrotum, its contained testis cannot be manipulated into it. Browne [19] described the superficial inguinal pouch as lying anterior to the external oblique fascia just superior to the external inguinal ring. The roof of the pouch is formed by Scarpa’s fascia and the posterior wall by the external oblique aponeurosis. Essentially, it is the space created by the PV in the groin and is limited by the extension of the external spermatic fascia from the external ring. Previously, an UDT in this position has been labelled as being ‘ectopic’. But today this term is generally restricted to the ‘truly’ ectopic testis (see Sect. 4.1.4) [20]. It is not known, however, whether the superficial inguinal pouch is caused simply by passive deflection of the testis and PV or whether the gubernaculum actively migrated in the wrong direction and thereby failed to enter the neck of the scrotum. Sometimes the gubernaculum is found to be firmly fixed medially towards the symphysis or upper neck of the scrotum, which suggests deflection rather than ectopic migration.

4.1.4 Ectopic Testes

The truly ectopic testis has descended to a position other than the scrotum and is described as being femoral, perineal (Figs. 4.1b and 4.3), pubopenile, or transverse (crossed) testicular ectopia. The perineal testis is located in the perineum or high on the medial aspect of the thigh lateral to the entrance of the scrotum. Its significance is that unless specifically looked for, it can easily be missed at clinical examination and result in an erroneous conclusion of an impalpable or absent testis. The testis may be positioned a long way beyond the external ring and even the scrotum and on some occasions lies not far from the anus (Fig. 4.3). Interestingly, the first successful orchidopexy described by Annandale in the British Medical Journal in 1879 was performed in a 3-year-old boy with an ectopic testis in the perineum [21]. The indication for surgery was to avoid future inconvenience when horse riding. Variants of ectopia include the so-called pubopenile testis, which lies at the base of the penis in a more medial position than the normal line of descent, and the crural or femoral

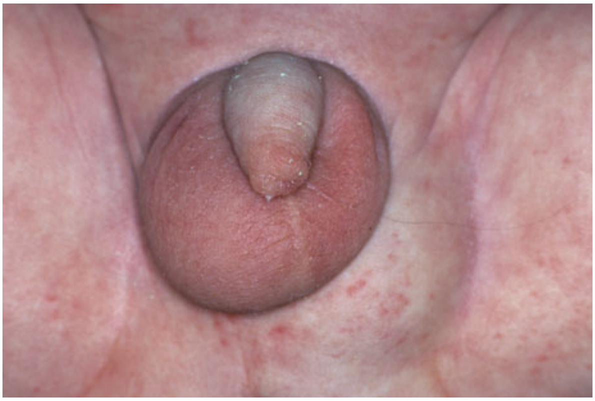

Fig. 4.3 Perineal ectopic testis

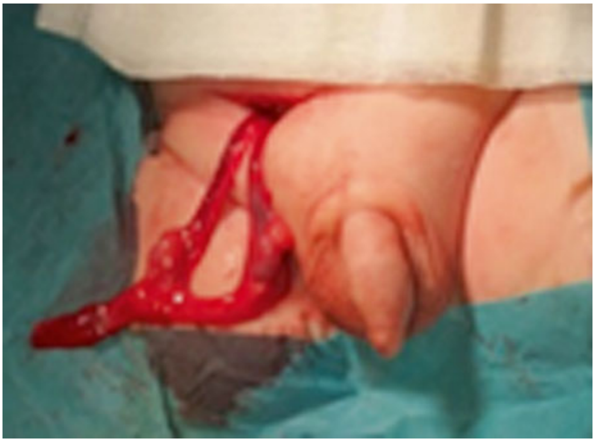

Fig. 4.4 Transverse testicular ectopia. Gubernacula of the two testes are fused (Reproduced with permission from Ref. [31])

testis, which is more obviously in the upper thigh. Occasionally the femoral ectopic testis has descended through the femoral canal rather than the inguinal canal. These ectopic positions of the testes, although rare, must be looked for in any child in whom the location of the testis is not immediately apparent.

4.1.4.1 Transverse Testicular Ectopia

Transverse testicular ectopia (crossed testicular ectopia) is an extremely rare but well-recognised entity in which the clinical findings are those of a hernia on one side and an impalpable testis on the other [22] (Fig. 4.4). The testis on the side of the hernia is normally found fully descended in the scrotum. The characteristic features of true descended crossed ectopia of the testis are (i) two testes found on one side with no testis on the other side; (ii) the testes identical in size and appearance and each has its own epididymis, vas deferens, and testicular vessels; (iii) and an associated hernia on the side of the two testes with no hernia on the contralateral side [23]. Genitourinary developmental abnormalities have been documented in 20 % of the cases in the form of defective Müllerian regression (rudimentary uterus), common vas deferens, seminal vesicle cyst, and bilateral renal dysgenesis [24–27]. Müllerian duct retention may be an important factor in its aetiology. Along with persistence of the Müllerian ducts, the female homologue of the gubernaculum, the round ligament, which normally tethers the uterus, fallopian tubes, and ovaries, is extremely long. Elongation of the round ligament in persistent. Müllerian duct syndrome allows greater movement of the testes, and without a short gubernacular cord, there is nothing to guide the testis into the correct inguinal canal (see Fig. 2.8).

Other theories have been proposed in an attempt to explain the aetiology of this rare anomaly. Berg [28] thought that the two testes arose from the same germinal ridge. Josso [29] suggested various anatomical factors that may result in such an anomaly: defective implantation of the gubernaculum, obstruction of the inguinal ring, and development of adhesions between the testes and adjacent structures. A retroperitoneal lymphatic malformation also has been described to cause transverse testicular ectopia [30]. Despite this wide variety of theories, the exact mechanism for the aetiology of this condition is still not fully understood [31].

4.1.5 The Retractile and Ascending Testis

Retraction of the testis into the upper scrotum (or even higher) is a normal phenomenon for regulating the temperature of the testis in children and is also a protective reflex. The cremasteric reflex which causes retraction can be invoked by cold temperature, anxiety, nervousness, or local stimulation, particularly in the region of the cutaneous distribution of the femoral branch of genitofemoral nerve (GFN) (Fig. 4.5). The sensitivity of the reflex varies between children and with age. At birth, the cremasteric reflex is either absent or extremely weak [32] and, between 3 and 9 years, is most pronounced. The testis can appear to be out of the scrotum for so much of the time that differentiation from true non-descent may be difficult and require periodic re-examination. The authors consider that while transient retraction of the testis is normal in school-age children, a testis described as ‘retractile’ is in a grey zone between a normal testis that is descended and one developing ‘ascent’ or becoming an ‘acquired’ UDT. It should be noted that paediatric surgeons have not reached complete agreement as to exactly what constitutes a ‘retractile’ testis. Most clinicians agree that the ‘retractile’ testis is a descended one, although careful follow-up is required and occasionally it may produce a surprise. Most think that rectractility reflects normal contraction of the cremaster muscle and has a direct relationship to age, but some may become ascending testes.

In order to distinguish between palpable UDT and retractile testes, the middle of the testis as a reference for each position has been used: suprascrotal, including inguinal and nonpalpable testes; upper portion of the scrotum; or lower portion of the scrotum. If a testis spontaneously assumes a suprascrotal position and cannot be pulled down into the scrotum, it is diagnosed as an UDT. If the testis is in a

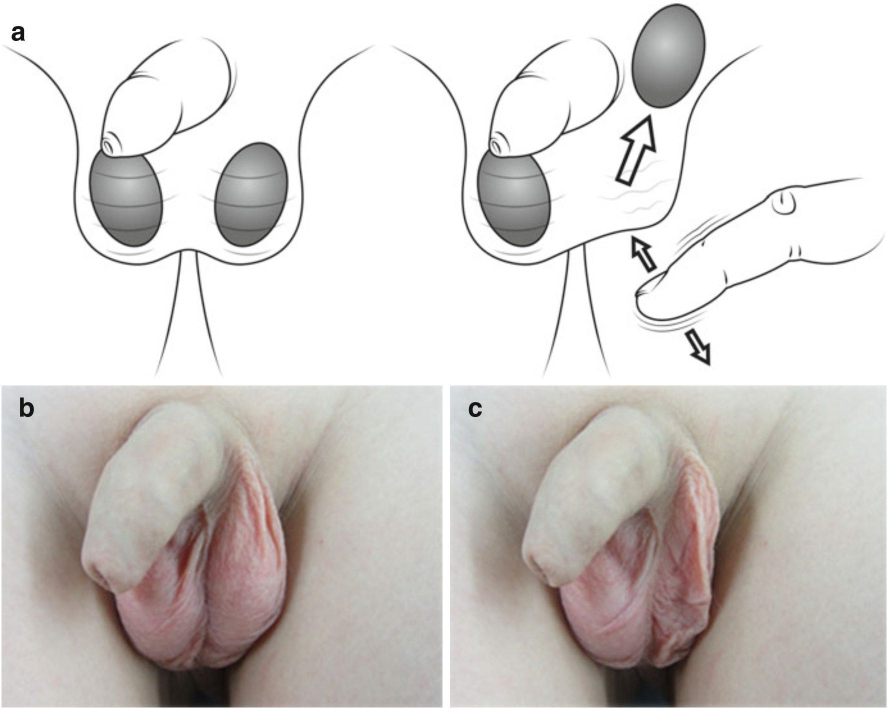

Fig. 4.5 (**a**) The retractile testis and reflex contraction of the cremaster muscle on stimulation of the inner side of the thigh (the cutaneous distribution of the genitofemoral nerve). (**b**) The appearance of the scrotum before eliciting the cremaster reflex. (**c**) The appearance of the scrotum after the reflex (Photos kindly provided by Dr. Zacharias Zachariou, Professor of Pediatric Surgery, University of Nicosia, Cyprus)

suprascrotal position and can be pulled down to the upper portion of the scrotum but does not remain there after exhausting the cremasteric activity, it is also defined as an UDT. If it remains in the upper or lower part of the scrotum after the traction is released, the patient has a retractile testis [33]. Ten to 50 % of patients referred to paediatric surgical units for treatment are diagnosed as retractile testis depending on age at referral and catchment area [34, 35]. Recognition of this condition is important, because it is generally accepted that the truly retractile testis requires no therapy, because the fertility potential of boys with retractile testes is usually considered to be normal [36]. However, some retractile testes are almost never spontaneously in the scrotum during childhood, with the ability of late spontaneous descent at puberty only. Patients with such testes bilaterally have been shown to have impaired fertility [37], and it may be acceptable to operate upon these testes early in order to possibly improve fertility [38]. In a recent study, 23 % of the patients with retractile testis required operation during the 3-year median follow-up, because the testis became cryptorchid or decreased in size [39].

A retractile testis which can only reach the high scrotal position is of much greater concern than one which assumes a low scrotal position.

4.1.6 The Ascending Testis

There is no clear and well-defined distinction between severely retractile testis and an ‘ascending’ testis. The latter has been documented to be descended in the scrotum within the first year of life and then reascended [40]. With somatic growth, the cord remains short, retracting the testis up. It has been postulated that the cause of this delayed ascent with growth is failure of the PV to involute, which leads to failure of the spermatic cord to elongate in proportion to the growth of the boy [41] (Fig. 4.6).

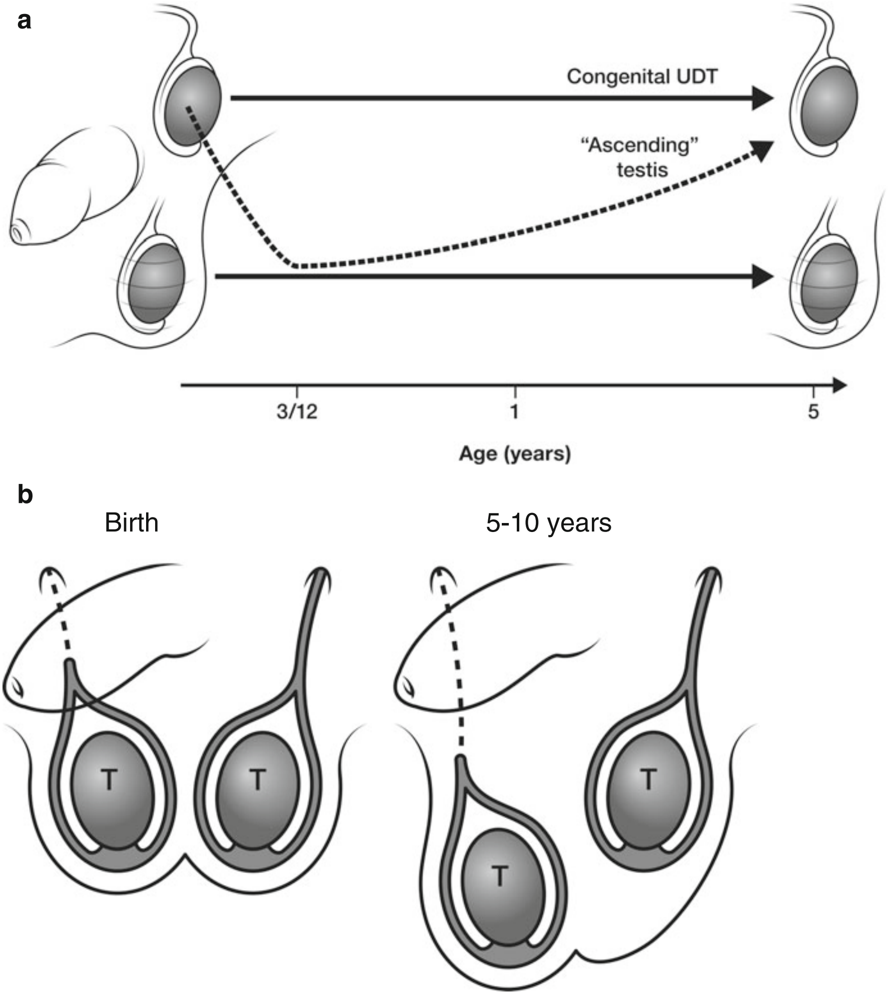

Fig. 4.6 (**a**) The presentations of congenital versus acquired undescended testes (UDT). The testis descended in infancy assumes a higher position later in childhood in acquired UDT, while congenital UDT is never in the scrotum. (**b**) Potential explanation for the ‘tight cord’ in ascending testis, which may be caused by failure of the processus vaginalis to completely disappear after birth, leaving an inelastic fibrous remnant preventing elongation of the vas and vessels

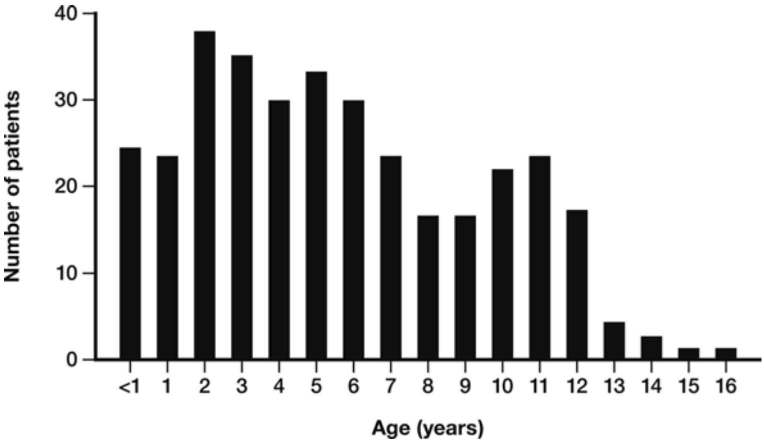

Fig. 4.7 Age distribution in 350 boys admitted for orchidopexy at the Royal Children's Hospital, Melbourne (Redrawn from Fenton et al. [47])

The correlation with a patent PV or fibrous remnant has been discussed [39, 42]. Also significant retractility is considered to be a risk factor for testicular ascent [43]. The potential for this condition makes it mandatory that intrascrotal testicular location be confirmed by periodic physical examination up to and through puberty. Ascended testes contribute to 20–60 % of operative cases [42, 44, 45]. In a cohort study, 1.5 % of the 3-year-old boys had been operated on or followed for cryptorchidism, which corresponds to 1.6 % being cryptorchid at an age of 3 months [46]. This study also showed that 40 % of the testes that were cryptorchid at birth and had spontaneous postnatal descent reascended to a suprascrotal position, possibly due to a higher grade of retractility. These data suggest that subsequent operation for ascending or retractile testes may explain the current frequency of 3 % of boys having surgery for cryptorchidism before the age of 15 years in a British study [46]. There are so far no strict guidelines regarding the optimal timing for operating on the ascending testis. However, children are often seen between 8 and 11 years, when the abnormality is most marked and anxiety about subsequent fertility leads to consultation. In a review of boys coming to orchidopexy at the Royal Children's Hospital in Melbourne, where 350 orchidopexies were performed per year, a significant percentage underwent surgery between 8 and 11 years of age (Fig. 4.7) [47, 48].

4.1.7 Acquired UDT

This term is used for testes that were previously in a normal scrotal position but have permanently achieved a fixed suprascrotal position. A complication after early inguinal hernia repair may be the cause, but frequently the term is used synonymously with ascending testis [20].

4.2 The Incidence of Undescended Testis (UDT)

The most widely quoted study investigating the incidence of UDT in the community is by Scorer [49] who surveyed more than 3,500 male infants and found a 4.3 % incidence of UDT. In full-term infants weighing more than 2,500 g, the incidence of cryptorchidism was 2.7 % compared with 21 % in premature infants (see Sect. 4.3). In an earlier study by Bishop [50], as many as 10 % of newborn males were recorded as having cryptorchidism.

Generally it is difficult to compare the frequency of cryptorchidism in different publications [51, 52], as the definition of cryptorchidism varies. One can readily define an UDT as one not being in the scrotum [53]. However, some testes are not in the scrotum when the examination starts but can be brought down to some degree. Some authors even include high scrotal testes (that can be manipulated to the bottom of the scrotum but immediately return to a higher but still scrotal position), into the group with congenital UDT [54]. Estimating the position of the UDT will always be partly subjective, since it is on a mesentery within the tunica vaginalis. In addition, the frequency of UDT in a population is dependent on birth weight. Premature boys have a significantly increased risk of cryptorchidism [46, 54–56], possibly due to the early delivery itself. However, in these preterm boys, the testes usually descend postnatally, and most will not have cryptorchidism by the due date [55].

In the literature, the incidence of UDT at birth for premature and/or infants with birth weight (<2,500 g) varies from 1.1 % to 45.3 % (most often around 20–30 %) and bilateral presentation in 50–75 % [43].

To facilitate comparison, several large series have addressed the incidence of congenital isolated cryptorchidism in newborns >2,500 g. Including only those males born with a birth weight >2,500 g, the incidence of cryptorchidism in studies over the last 50 years has been noted to be 1.8–8.5 % and is bilateral in about 30 % of the cases (Table 4.1) [40, 46, 49, 54–61]. Over the years, the prevalence of cryptorchidism in full-term males seems to be quite stable and with only small differences between geographical areas. However, at first glance, the study by Boisen et al. [54] showed a clearly conflicting result. They identified cryptorchidism in 8.5 % of full-term newborn Danish males with a birth weight >2,500 g but in doing so included 6.5 % with high scrotal testes that could be manipulated to the bottom of the scrotum but immediately returned to a higher but still scrotal position. They introduced new terminology such as ‘severe’ cryptorchidism, which then has the same prevalence in those males born with a birth weight >2,500 g, as seen in other Danish studies—namely ~2 %. So they seem to describe a mild form of cryptorchidism including scrotal testes that they identify as abnormal. We are not convinced that the so-called ‘high scrotal’ testes have been included in previous Danish prevalence studies on newborns. Many testes return to a higher scrotal position when palpated, especially in a cold environment. Thus one cannot conclude that the prevalence of these proposed abnormal scrotal testes has changed over time. We regard it as much more important that Cortes et al. [57] identified a 1.9 % prevalence of UDT in Danish newborn males with birth weight >2,500 g in 2007 versus 1.8 % in the Buemann et al. [56] study from 1961. Thus, a true slight increase cannot be

Table 4.1 Incidence of congenital UDT in newborn boys with a birth weight >2,500 g

References	Country	Year of publication	Total n	Prevalence at birth	Bilateral %	Assessment at follow-up (1–4 years)—prevalence
Scorer	UK	1964	3,612	2.7 %	11 %	–
Villumsen et al. Buemann et al.	Denmark	1966	4,500	1.8 %	29 %	0.7 %
Hirasing et al.	Netherlands	1982	1,781	2.0 %	–	–
John Radcliffe Hospital	UK	1992	7,400	4.1 %	34 %	1.6 %
Berkowitz et al.	USA	1993	6,935	2.2 %	–	1.0 %
Thong et al.	Malaysia	1998	882	2.4 %	29 %	–
Ghirri et al.	Italy	2002	9,343	3.4 %	–	1.5 %
Boisen et al.	Finland	2004	1,426	2.1 %	–	–
Boisen et al.	Denmark	2004	1,005	8.5 %	–	–
Preiksa et al.	Lithuania	2005	1,135	4.6 %	31 %	–
Cortes et al.	Denmark	2008	1,088	2.1 %	15 %	1.6 %

excluded. Also the study by Preiksa et al. [61] from 2005 showing a prevalence of 4.6 % includes high scrotal testes (that could be manipulated to the bottom of the scrotum but immediately returned to a higher position) in the group with cryptorchidism. So, the overall prevalence of cryptorchidism in males born with a birth weight >2,500 g varies between 1.8 % and 4.1 %, depending on genetics, study design and differences in definitions and classifications, and exclusion of 'scrotal UDT'. Importantly, these figures have not increased over time.

Of full-term males noted to have cryptorchidism at birth, spontaneous descent is reported to occur in some patients usually by age 1–3 months, with descent up to 6–9 months occurring rarely, so that when followed up at the age of 1 year, the prevalence of cryptorchidism is generally lower (Table 4.1). Spontaneous postnatal descent in preterm and full-term boys occurs more often in bilateral than in unilateral cases and more often in smaller boys at birth. This is in accordance with the findings at orchidopexy in childhood. In a review of 10,575 orchidopexies, only 22 % of the boys had bilateral UDT [8].

The observation that testes thought to be completely descended at birth may 'ascend' to a suprascrotal position with time was noted by Villumsen and Zachau-Christiansen in 1966 [40]. In that series, 69 of 4,300 boys (1.6 %) had unilateral ($n = 51$) or bilateral ($n = 18$) ascent of testes from a normal scrotal position at birth to a higher position by age 3 years (Fig. 4.8). Others have noted this same phenomenon in case reports with well-documented longitudinal data [62]. Later in

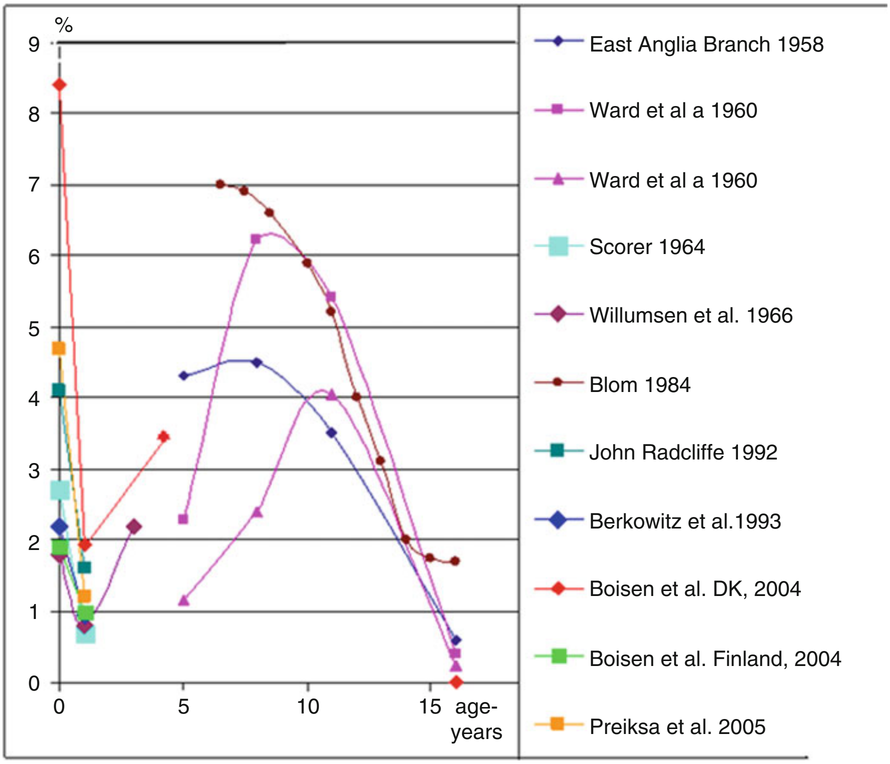

Fig. 4.8 Prevalence of cryptorchidism (%) (*y*-axis) in relation to age of the boys (years) (*x*-axis) in accordance to different studies of the literature (Modified after Thorup and Cortes [38])

childhood, the ascended testis can be extremely difficult to discriminate from retractile testes, and in addition, the previous scrotal position may be hard to verify. Agarwal et al. [63] retrospectively reviewed the charts of 122 boys (mean age 5.4 years) who were referred for a suspected UDT and were found to have a retractile testis. The retractile testis was defined as a suprascrotal testis that could be manipulated easily into the scrotum and remained there without traction until the cremasteric reflex was induced. The boys were followed by annual examinations, to demonstrate the presence of retractile, descended (nonretractile) or UDT, and the presence or absence of a taut or inelastic spermatic cord. Of 204 retractile testes, 61 (30 %) descended (became nonretractile), 66 (32 %) became UDT, and 77 (38 %) remained retractile. Of the 62 retractile testes with a taut or inelastic spermatic cord, 35 (56 %) became UDT. Boys in whom UDT developed were a mean of 4.9 years old. The authors concluded that a retractile testis is not a normal variant given the associated 32 % risk of becoming an ascending or acquired UDT. These conclusions are consistent with our own view that the 'retractile' testis is in a grey zone between a normally descended testis and an acquired, ascending testis.

There are few studies following UDT nonoperatively through childhood and puberty [38, 64, 65]. There is no doubt that a late spontaneous descent occurs in some cases, probably mainly in retractile testes. With a peak around 7–8 years of age, 5–7 % of boys do not have both testes in a satisfactory scrotal position when investigated at school examinations, but most of these testes will descend during puberty. Interestingly, Ward and Hunter [64] found a higher prevalence of UDT when examining the boys in school compared with examining the same boys in the medical office. This illustrates some of the diagnostic problems. Previously retractile testes were considered a normal variant, but this is probably not true for all retractile and late spontaneously descended testes. Pathological studies provided evidence that some retractile testes may be abnormal. Han et al. [66] found that although retractile testes have a significantly higher average number of spermatogonia than cryptorchid testes, they have the same degree of tubule degeneration, suggesting that retractile testes undergo some abnormal histological change. Another study shows that once a previously retractile testis undergoes testicular ascent, it acquires the same decrease in total and differential germ cell count as primary UDT [67].

Rasmussen et al. [37] followed a large cohort of boys with bilateral cryptorchidism nonoperatively with annual examinations through puberty. They reported the long-term fertility potential of 45 men from this group whose testes were at the external ring, superficial inguinal pouch and/or prescrotal positions but descended spontaneously between ages 10 and 16 years (mean 12). In these men, the testes were reportedly dependent in the scrotum but were frequently borderline or subnormal in size (75 %) and associated with subnormal sperm concentration (53 %). It is noteworthy that when comparing the Danish data on newborns with cryptorchidism and high scrotal testes included from 2004 by Boisen et al. [54], along with the Danish data on school children born in 1940–1966 by Blom [65], they both find a 7–9 % prevalence of abnormal testes. This may indicate that in some newborns there may be scrotal testes that are abnormal from the perspective of fertility potential. It is important to remember that most infertile men have no history of corrected cryptorchidism, but some may have congenital endocrinopathy. Some high scrotal testes may be associated with later infertility; however, there appears to have been no change in prevalence over the last 50 years.

The aforementioned factors may explain why orchidopexy rates in different countries, such as Denmark, often exceed the prevalence of congenital cryptorchidism. Ascended testes contribute 20–60 % of orchidopexies [42, 44, 45, 68, 69]. Also significant retractility is considered to be a risk factor for testicular ascent [43], and the orchidopexy rate has not changed significantly in different publications within the last 40 years. The cumulative orchidopexy rate in different countries is stable around 2.4–3.8 % [47, 70–74], with a minor transient increment of orchidopexy rates in Denmark and the UK in 1980–1990 [70, 75]. Also in New York, the orchidopexy rate has been stable during the last decades [76]. In the State of Victoria, Australia, there has been a true decline in the number of orchidopexy operations done in children between 1999 and 2006. This may represent a true decline in the incidence of disease, a failure of diagnosis, or a failure of management [77]. So with an overall worldwide prevalence of UDT within the first years of life of 1–2 %, the orchidopexy rates around 2.4–3.8 % fit well with the figure that half the orchidopexies in childhood are performed on ascending or severely retractile testes.

4.3 What Causes Cryptorchidism?

The common causes of cryptorchidism remain essentially unknown. Even though reproductive hormones are involved in testicular descent, hormone deficiency does not necessarily appear to be a common cause of the majority of UDT.

Changes in testicular endocrine function related to cryptorchidism have been documented from early puberty to adulthood [78, 79], whereas results in childhood are controversial [80–84]. In 3-month-old cryptorchid boys, inhibin B values were decreased and FSH increased [83] depending on the severity of the condition. High scrotal testes and cryptorchid testes with spontaneous postnatal descent showed a subtle impairment of the pituitary–gonadal axis [83]. In older boys, however, 75 % of boys with unilateral UDT, inhibin B serum levels were within the normal range [82]. Inhibin B was low in some boys with a low number of germ cells at biopsy [80] [84] (see Chap. 6).

Increasing levels of inhibin B were reported in a substantial proportion of boys 6 months after successful surgery [84–86]. In adulthood, higher levels of inhibin B were found in men who underwent orchidopexy before 2 years of age than later [79]. In infertile men, lower inhibin B and higher FSH levels were found if there was a history of cryptorchidism [87, 88]. Based on published studies [86, 88, 89], approximately 40 % of bilateral cases and 10 % of unilateral cases may have a subtle impairment of gonadotrophin production. But a substantial proportion of cryptorchid patients may have increased gonadotrophin serum levels related to the feedback mechanism.

In a prospective case–control study, Fenichel et al. [90] assessed 180 boys born after 34 weeks' gestation—52 cryptorchid (48 unilateral, 4 bilateral; 26 transient, 26 persistent)—and 128 controls matched for term, weight, and time of birth. INSL3 and testosterone were measured in cord blood and compared in both groups as were other components of the pituitary–gonadal axis: LH, hCG, FSH, AMH, and SHBG. They found that INSL3 was decreased in cryptorchid boys ($P = 0{,}03$), especially transient cryptorchid ($P = 0{,}02$), while testosterone was unchanged as were the other hormones measured. INSL3 was significantly decreased ($P = 0{,}02$) in the group of 20 with nonpalpable testes compared with the group of 21 with palpable testes (15 suprascrotal, 5 inguinal, 1 high scrotal). In the whole population, INSL3 correlated positively with LH and negatively with AMH, but with no other measured hormones. So they concluded that INSL3 but not testosterone was decreased at birth in idiopathic cryptorchidism, especially in transient forms. This hormonal decrease may contribute to the impaired testicular descent along with genetic and anatomical factors.

Low birth weight is a well-known association with cryptorchidism and may be related to impaired placental function. Testicular descent is at least partially dependent on fetal testicular testosterone, which, in turn, is initiated and maintained by hCG produced by the placenta [70, 91, 92].

Though the risk of cryptorchidism generally is elevated in low birth weight, this was not the case in twins studied by Cortes et al. [57]. They found a frequency of cryptorchidism in 2.6 % of twins compared to 2.4 % in singletons, despite the fact that the frequency of a birth weight below 2,500 g was 51 % in twins and 4.9 % in singletons. So the special hormonal influence of prenatal twins, which may be related to the greater and more competent placenta, may lead to a lower risk of cryptorchidism [55, 93]. Equally, Biggs et al. [91] found an elevated risk of cryptorchidism in cases with placental abnormalities.

Interestingly, in a study of 69 boys with proximal hypospadias, Sekaran et al. [94] found that among those boys with proximal hypospadias and UDT, there was a higher incidence of premature birth and intrauterine growth restriction than among boys with proximal hypospadias and descended testes. The coexistence of growth restriction and genital anomalies suggested that this association is due to shared causes, such as placental insufficiency with impaired hCG level and androgen deficiency in early pregnancy [94].

4.3.1 Familial and Genetic Factors

Familial aggregation in population-based studies suggests moderate genetic susceptibility and also implicates the maternal environment as contributory to cryptorchidism risk [95, 96]. In a population-based study of 1,024,500 boys, concordance rates of cryptorchidism in the groups were as follows: boys with no relation 3.2 % (95 % confidence interval 2.7–3.6 %), paternal half-brothers 3.4 % (2.3–4.7 %), maternal half-brothers 6.0 % (4.5–7.7 %), full brothers 8.8 % (8.3–9.8 %), dizygotic twin brothers 24.1 % (16.0–33.6 %), and monozygotic twin brothers 27.3 % (15.5–41.2 %) [95]. Diagnosis concordance rates were similar in monozygotic and dizygotic twins (27 % and 24 %, respectively), but when analyses were limited to those receiving surgical treatment, rates were lower for dizygotic twins (17 %), suggesting that environmental factors may be more relevant in spontaneously resolving cases [95]. The higher concordance rate in dizygotic twin brothers compared to full brothers emphasises the impact of the maternal/placental environment.

Previous smaller studies reported a five- and seven- to tenfold increased risk of cryptorchidism in fathers and brothers, respectively, of affected (as compared to unaffected) subjects [97–99], and also supported the possibility that maternal factors, or X-linked risk alleles, influence expression of the phenotype. The latter observation is in accordance with the findings in the aforementioned study by Jensen et al. [95] that the concordance rate in maternal half-brothers was higher than the concordance rate in paternal half-brothers. These levels of familial risk exceed those for many complex diseases, predicting the potential for greater success in genome-wide analyses [100].

The aetiology of cryptorchidism is likely multifactorial, but associated genetic loci remain largely unknown. The major pathways required for testicular descent are regulated by INSL3 and androgens, Leydig cell-derived hormones that control the development of the fetal gubernaculum. Exonic variants of INSL3, or its receptor, relaxin/insulin-like family peptide receptor 2 (RXFP2) are rare in cryptorchidism cases, and their functional significance is poorly defined [101]. Reports linking potential candidates in homeobox (HOXA10, HOXA11) or sex steroid receptor (ESR1, AR) genes to cryptorchidism susceptibility have been inconsistent or unconfirmed in additional populations [102–113]. In single, small series, cryptorchidism was linked to variants in aryl hydrocarbon receptor-associated genes (ARNT2, AHR) and to the gene encoding steroidogenic factor 1 (NR5A1) [114, 115].

Dalgaard et al. [116] performed a genome-wide association study (GWAS) and further analysed their data using systems-biology methodology to identify genetic markers linked to the phenotypic manifestations of the so-called testicular dysgenesis syndrome (TDS), a constellation of male reproductive abnormalities that includes cryptorchidism, hypospadias, testicular cancer, and infertility. Although this unbiased approach did not identify any signals of genome-wide significance, it was not sufficiently powered (138 and 103 cases in the discovery and replication cohorts, respectively) for the discovery of loci specifically associated with isolated cryptorchidism. Multiple suggestive loci that were reported in the discovery phase for the entire TDS cohort also showed at least nominal significance in the cryptorchidism discovery subset but were not confirmed in the replication phase. However, rs12082710, an intronic single nucleotide polymorphism (SNP) of TGFBR3, and rs388226, a SNP of BMP7, showed possible association with all phenotypes of TDS for discovery but for testicular cancer and cryptorchidism only for replication. This TGFBR3 gene is of interest because of its association with testicular dysgenesis and abnormal Leydig cell development in a transgenic mouse model [117]. Considering the multilocus aetiology of cryptorchidism and the possibility that exposure to combinations of environmental chemicals with anti-androgenic and/or oestrogenic activity may contribute to risk [118], it is not surprising that limited studies thus far have failed to convincingly identify associated genomic loci.

A genome-wide association study on a well-described population of Siberian Huskies found six putative genomic regions containing candidate genes for canine UDT that are functionally related to extracellular matrix remodelling [119], which may be important for gubernacular remodelling during migration.

4.3.2 Environmental Factors

Based on epidemiological, experimental, and wildlife evidence, it has been hypothesised that the prenatal exposure to endocrine disrupting chemicals (EDCs) might be causally related to congenital cryptorchidism [120, 121]. However, roughly 800 chemicals are known or suspected to interfere with the endocrine system. Due to continuous background exposure to this mixture of chemicals throughout life, it has proven difficult to establish associations between prenatal exposure to a single group of chemicals and cryptorchidism in humans. Persistent organic pollutants (POPs) are a group of endocrine disrupting chemicals that are toxic, persistent, able to accumulate at the top of the food chain, and able to move long distances by natural processes in soil, water, air, and biota. Of these chemicals, polychlorinated biphenyls (PCBs) have been used in transformer oils, in capacitors, and as heat-transfer agents until the mid-1980s, whereas polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs or 'dioxins') are formed unintentionally in the synthesis of chlorinated substances (including PCBs) and during incineration of municipal waste. Unlike the aforementioned POPs, some congeners of polybrominated diphenyl ethers (PBDEs) are still actively produced and used as flame retardants in electrical devices, furniture, and textiles [122]. In Northern Europe, trend studies show declining body burdens of PCBs and PCDD/Fs after the 1980s [123], whereas the body burden of PBDEs was increasing rapidly until the early 2000s [124]. Today, humans are exposed to PCBs, PCDD/Fs, and PBDEs via breastfeeding and consumption of fish, meat, and dairy products [125–127] and to PBDEs also via inhalation and ingestion of indoor dust [128]. PCBs, PCDD/Fs, and PBDEs are excreted to lipid-rich breast milk, and the exposure per kilogram body weight is high during lactation [125, 128]. There is some evidence for an association between levels of PCBs, PCDD/Fs, and PBDEs and cryptorchidism in humans [129–131], although in other studies, associations have not been found [118, 132–134].

Well-known occupational risk factors such as direct exposure to pesticides among pregnant females employed in greenhouses have shown impact on prevalence rates on cryptorchidism [135, 136]. Hakonsen et al. [137] did an extensive review of the literature on maternal cigarette smoking during pregnancy and cryptorchidism. Based on 20 epidemiological studies and a meta-analysis [138] investigating the association between maternal cigarette smoking and cryptorchidism, Hakonsen et al. [137] concluded that although the majority of studies found no association, the two largest case–control studies as well as a large pregnancy cohort study observed an increased risk of cryptorchidism in offspring of cigarette smoking mothers after adjustment for potential confounders. Furthermore, the meta-analysis indicated a small increased risk for cryptorchidism [138]. Thorup et al. [70] found that within the group of cryptorchid boys, maternal smoking of >10 cigarettes daily increased the risk of the condition being bilateral as opposed to unilateral. In offspring exposed to cigarette smoking in utero, a reduced concentration of estrone and free beta-human chorionic gonadotrophin (beta-hCG) in umbilical cord blood have been reported, which may indicate an altered hormonal exposure of the fetus due to insufficient placental beta-hCG production [139]. One may speculate that the previously (Sect. 4.2) described minor transient increment of orchidopexy rates seen in Denmark and the UK in 1980–1990 [70, 75] may be related to the peak of female cigarette smoking in both countries in the late 1970s as the age of surgery for cryptorchidism at that time was 5–10 years old for the majority of the boys. Maternal gestational diabetes and intrauterine exposure to mild analgesics have also been considered as risk factors for development of cryptorchidism [140, 141].

Conclusion

The classification of UDT is becoming much clearer with the recognition that many 'retractile' testes develop into ascending, acquired UDT. Retractile testes should now be treated with caution, as they are in a grey zone between normality and abnormality.

The incidence of UDT was thought to be increasing, but recent studies suggest increased frequency may be related to the definition of UDT as some series include high scrotal testes as ‘undescended’.

The aetiology remains mostly unknown and is likely to be multifactorial, but environmental disruptors may act on several different steps in the complex descent process. Genetic screening has implicated muscle development pathways and connective tissue remodelling, and we are hopeful the near future will reveal a clearer picture of the presumed multiple causes of UDT.

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Cryptorchidism and Associated Anomalies

5

There are a number of recognised abnormalities and syndromes in which the incidence of cryptorchidism is significantly higher than in the general population. This chapter discusses some of those conditions and describes the reasons why they may be associated with cryptorchidism.

Cryptorchidism is associated with other congenital abnormalities in less than 20 % of cases, but when present, then most often related to abnormalities of the midline and caudal developmental fields [1]. The defects may be asymmetrical and the full expression may not be seen until later in fetal life [1, 2].

5.1 Caudal Developmental Field Abnormalities

Association between cryptorchidism and abnormal caudal development is relatively more common than that of isolated cryptorchidism and hypospadias. The close relationship between cryptorchidism, imperforate anus, and abnormal caudal development had been described in detail by Cortes et al. [1] (Fig. 5.1). In a series of 34 cryptorchid boys under 3 years, caudal abnormalities, malformations, and dysplasias of the kidneys, the ureters, and the spine from T10 to S5 were the predominant abnormalities in 18 % of these cryptorchid individuals [3]. Also, autopsy data show coexisting urogenital abnormalities in 31 % of cryptorchid boys and coexisting urological abnormalities in 14 % of cryptorchid adults [4]. The cryptorchidism was on the same side as the urological abnormalities in 93 % of cryptorchid boys [5]. The position and histology of UDT were independent of the abnormalities encompassed by the association [5–7]. Abnormal placental–fetal circulation implicated as a cause of the spectrum of so-called human caudal malformation sequences has been hypothesised many years ago [8]. The most outstanding variety of caudal developmental field malformation is tritonomelia (the male version of sirenomelia). Both have cryptorchidism, urinary tract abnormalities, spine defects, and lower limb fusion [5].

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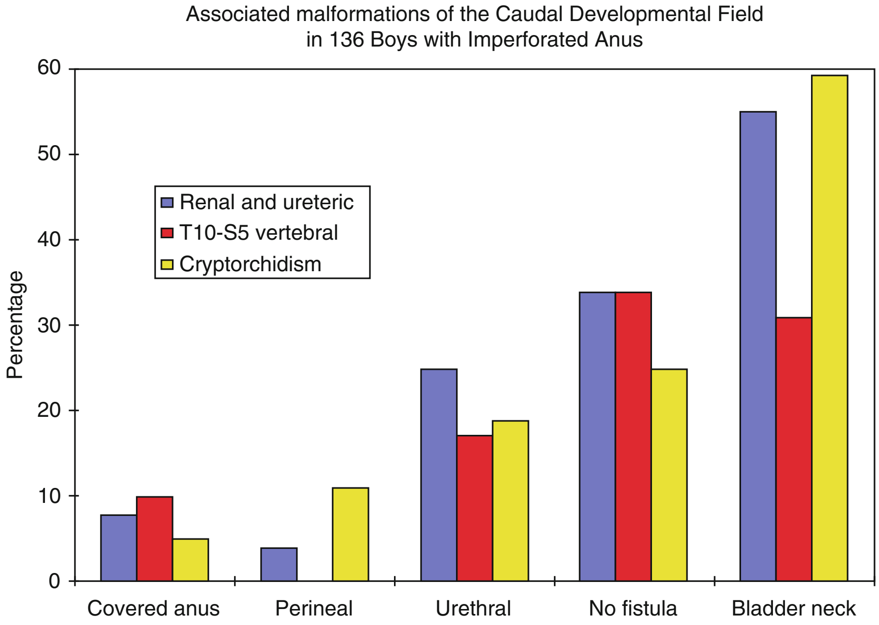

Fig. 5.1 Associated malformations of the caudal developmental field in 136 boys with imperforate anus classified according to the severity of the malformation (level of fistula)

5.2 Hypospadias and the Testicular Dysgenesis Syndrome

Skakkebaek et al. [9] have hypothesised that poor semen quality, testis cancer, UDT, and hypospadias are symptoms of one underlying entity—the so-called testicular dysgenesis syndrome (TDS) [9]. They have suggested that an imbalance between oestrogens and androgens during fetal life may be crucial. Initially, the oestrogen hypothesis argued that the increase of reproductive abnormalities in human males may be related to increased oestrogen exposure in utero [10]. This hypothesis has been expanded to include endocrine disruptors, which include environmental toxins that can disrupt the hormonal balance of the fetus and thereby disturb sexual differentiation either by an oestrogenic or an anti-androgenic effect [11]. Data also indicate that oestrogens can induce cryptorchidism and hypospadias by suppressing androgen production or action. Additionally oestrogen can induce cryptorchidism by suppression of insulin-like hormone-3 (INSL3) [12, 13].

Consistent with the TDS concept, hypospadias is indeed associated with cryptorchidism. In a Swedish study on hypospadias, 6 % of the boys had cryptorchidism on one or both sides [14]. However, although the odds ratio of hypospadias cases also having cryptorchidism equals approximately 5, the odds ratio of hypospadias with other congenital abnormalities, such as imperforate anus, is much higher (Table 5.1) [15]. The fact that trans-abdominal descent occurs

Table 5.1 The odds ratio of the association of hypospadias with other malformations (Aschim et al. [15])

Characteristics	Cases $N = 2382$	Controls $N = 235{,}542$	Crude OR	CL
Small for gestational age	378	18,948	2.16	1.9–2.4
Cleft palate (isolated)	6	107	5.56	2.4–12.6
Cleft + lip + evt. palate	12	394	3.02	1.7–5.4
Oesophageal atresia	3	43	6.91	2.1–22.3
Imperforate anus	8	40	**19.84**	9.3–42.4
Diaphragmatic hernia	3	65	4.57	1.4–14.5
Omphalocele/cord hernia	3	39	7.62	2.4–24.7

between 10 and 15 weeks of gestation, during the same critical period as penile development, may explain why hypospadias is seen in 4.3 % of boys with intra-abdominal UDT compared to 1.4–1.6 % in unselected cryptorchid boys [16, 17]. In this respect, it has to be emphasised that more than 98 % of cryptorchid boys have no hypospadias. The full expression of TDS is rarely seen except in a few individuals with abnormal 45,X/46,XY karyotype and other disorders of sexual development.

5.3 Prune Belly Syndrome

Prune belly syndrome is a rare condition which occurs almost exclusively in boys and consists of a redundant wrinkled (‘prune’) abdominal wall, dilatation of the entire urinary tract, and failure of descent of the testes. Bilateral intra-abdominal UDT are a universal finding (Fig. 5.2).

For many years, prune belly syndrome was thought to be a primary mesodermal defect [18, 19], but this concept did not account for the UDT. There is now mounting evidence that the cause of prune belly syndrome (PBS) is prenatal urinary obstruction [20–21], although in most cases, no site of obstruction can be identified postnatally [23]. Hutson and Beasley [23] have conjectured that the syndrome is due to a transient obstruction of the urethra between its glanular and penile parts and that this causes gross dilatation of the urinary tract, including the bladder. The degree of the distension of the bladder can be documented by ultrasound between 10 and 20 weeks’ gestation [24] and is such that the testes would be prevented from entering the inguinal canal by the peritoneal reflection of the expanding bladder completely obliterating the testes’ access to the inguinal canal [23, 25]. In addition to the separation of the inguinal canal from the peritoneum, it is probable, although unproven, that the grossly enlarged bladder causes disruption of the gubernacular apparatus. This would prevent growth of the processus vaginalis (PV) into the canal and make it impossible for the testis to descend, even after deflation of the bladder.

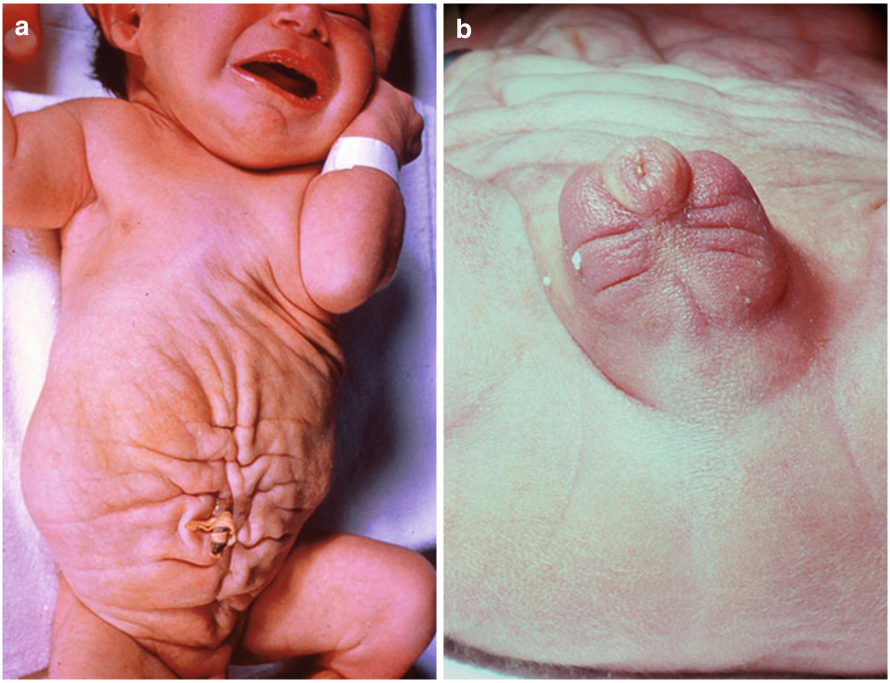

Fig. 5.2 Bilateral UDT are a universal finding in prune belly syndrome. (**a**) The wrinkled abdominal wall remains after relief of the gross urinary obstruction in utero. (**b**) The empty, hypoplastic scrotum

5.4 Posterior Urethral Valve

Cryptorchidism occurs in 12 % of boys with posterior urethral valve [26]. Although this is a rare report linking cryptorchidism and posterior urethral valve, it involved 207 children of whom 24 had UDT. Bilateral cryptorchidism occurred in 42 %, compared with about 25 % in the usual cryptorchid population. The authors suggest that the association may be the result of some common developmental mishap, perhaps of mesenchymal origin. Given the early developmental origin of posterior urethral valves from presumed failure of regression of the urethrovaginal folds of the pelvic urogenital sinus and the late fetal transinguinal descent of the testis, it is more likely that the high incidence of cryptorchidism occurs because of dilatation of the urinary tract proximal to the urethral obstruction, perhaps in the same way as is seen in the prune belly syndrome [23]. However, posterior urethral valve is also seen in rare cases associated with other midline developmental defects (e.g. agenesis of corpus callosum) and Down syndrome, both of which are also described with otherwise isolated cryptorchidism.

5.5 Exomphalos and Gastroschisis

In these conditions, there is a defect of the ventral abdominal wall (Fig. 5.3) that in males is associated with a high incidence of cryptorchidism [27, 28]. The incidence of cryptorchidism at birth and at 1 year in patients with gastroschisis was reported as 18 % and 15 %, respectively, and in those with exomphalos was 52 % and 33 %, respectively [28]. From these data, the authors concluded that in male infants there was an association between the abdominal wall defect and cryptorchidism and that it was consistent with a possible role for intra-abdominal pressure in the process of testicular descent. The inability of the fetus to generate an effective increase in intra-abdominal pressure contributed to failure of the testes to enter the inguinal canal and descend normally [29]. This explanation has not been accepted universally: for example, Hadziselimovic et al. [27] believe that the presence of concomitant brain malformations is significant and causes the cryptorchidism. Some of these malformations of the nervous system described, e.g. spina bifida, themselves have a potentially independent effect on testicular descent (see below). Interestingly spontaneous testicular descent after closure of the abdominal wall in gastroschisis has been observed in several cases, consistent with formation of a normal PV inside the gubernaculum.

5.6 Spina Bifida

Until 1981, cryptorchidism was not recognised as a significant problem in children with meningomyelocele [30], although many clinicians may have suspected the incidence of UDT in boys with spina bifida to be higher than that of the normal population. Kropp and Voeller observed cryptorchidism in 6 of 23 boys with spina

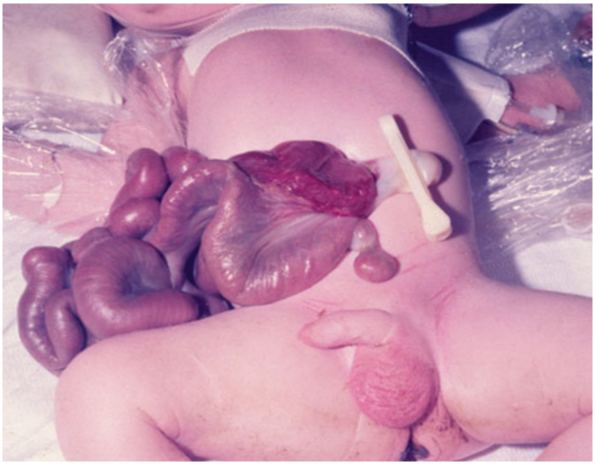

Fig. 5.3 Gastroschisis is commonly associated with UDT, which occasionally may herniate through the defect. In this infant, one testis is undescended and visible protruding through the abdominal wall defect

bifida. In two other studies [31, 32], a similarly high incidence of cryptorchidism has been reported in spina bifida: combined with a series of patients from the Royal Children's Hospital, Melbourne, this represents 15 of 85 boys (18 %) with UDT.

The level of the sensory and motor deficit affected the incidence of UDT, and lesions above L2 were found to have a greater association with cryptorchidism. Disruption of nerve root and spinal cord function in spina bifida is not always clear-cut or predictable in relation to the external appearance of the lesion or to its level, which may account for the variability of the observations [33]. Nevertheless, it would seem that the incidence of UDT is increased significantly in spina bifida, particularly where the lesion is at or above L3.

The most compelling evidence comes from the computerised database from the International Myelodysplasia Project, Seattle, through the kind assistance of David Shurtleff, MD. Of the 470 boys included in the file, the position of the testes and the level of the spina bifida lesion were recorded in 345, and 81 (23 %) had UDT. UDT were present, both unilateral and bilateral, in 19 % (37 of 186) of the low lesions, compared with 21 of 59 (36 %) in the high lumbar area. These data strongly support the proposal that abnormalities of the high lumbar cord are associated with a significant increase in cryptorchidism.

5.7 Cloacal Exstrophy

Postmortem examination of an infant born with cloacal exstrophy (Fig. 5.4) has provided some clues to a possible mechanism of failure of testicular descent in this condition [34]. On each side, an intra-abdominal testis was attached by the gubernaculum

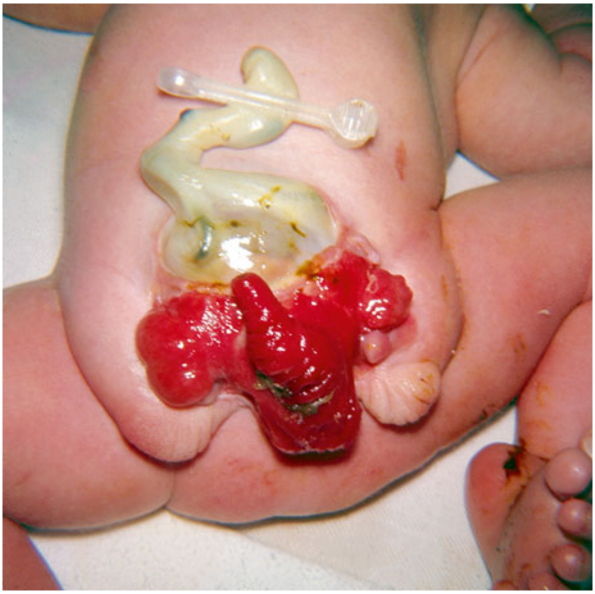

Fig. 5.4 Cloacal exstrophy associated with bilateral intra-abdominal testes

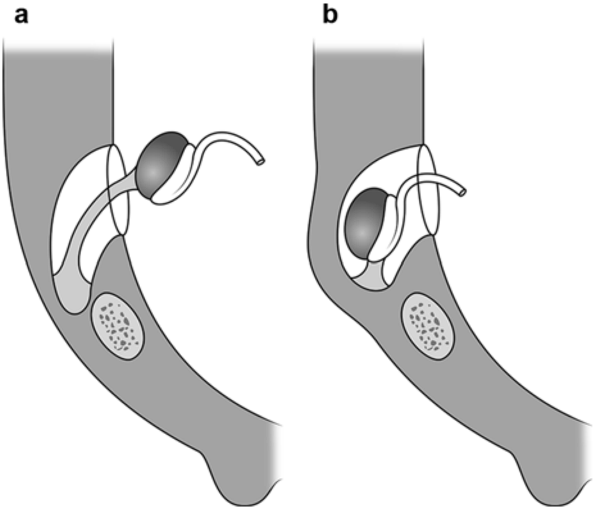

Fig. 5.5 Schema of the anatomy found in a boy with cloacal exstrophy. (**a**) Testis in an intra-abdominal position attached to the internal ring by a peritoneal fold containing gubernaculum. (**b**) The testis could be evaginated into the pouch to recreate the normal anatomy of the inguinal canal (Reproduced with permission from Hutson and Beasley [34])

to an evertable pouch in the lateral abdominal wall. The internal ring was located at the site of the pouch. Despite the severe pubic diastasis, the scrotum was located medially, far removed from the laterally placed inguinal canal. Each testis could be manipulated into the base of its pouch but was prevented from descending further by the tough fascia of the flank which separated it from the scrotum (Fig. 5.5). The testes apparently failed to descend beyond the inguinal canal because of their abnormal position. The tight fascial planes replacing the low-pressure pre-scrotal space outside the external ring may have prevented descent. This clinical example of mechanical failure of descent supports the hypothesis that a pressure gradient across the inguinal canal is required for normal descent to occur [35, 36]. This is consistent with the observation that external compression can delay testicular descent in rodents [37].

5.8 Cerebral Palsy

Several studies have shown that the incidence of ‘cryptorchidism’ in cerebral palsy is higher than expected [38–41]. The overall prevalence of cryptorchidism in post-pubertal males with cerebral palsy is reported as ranging from 41 % [39] to 54 % [40]. Although several possible aetiologies for these findings have been offered previously, including anomalies of the gubernaculum, Leydig cell atrophy, and decreased luteinising hormone response to luteinising hormone-releasing factor (LHRH), none of these has been demonstrated consistently in cerebral palsy [42]. One feature of cerebral palsy is the progressive spasticity of muscles with increasing age [43, 44]. By contrast, there is often little evidence of spasticity in infants at the time of diagnosis. Many muscle groups have been incriminated, and it would seem likely that the cremaster muscle also could be involved. This involvement would lead to increased cremasteric spasm and a relatively higher position of the testis with growth, especially in those boys with spastic diplegia.

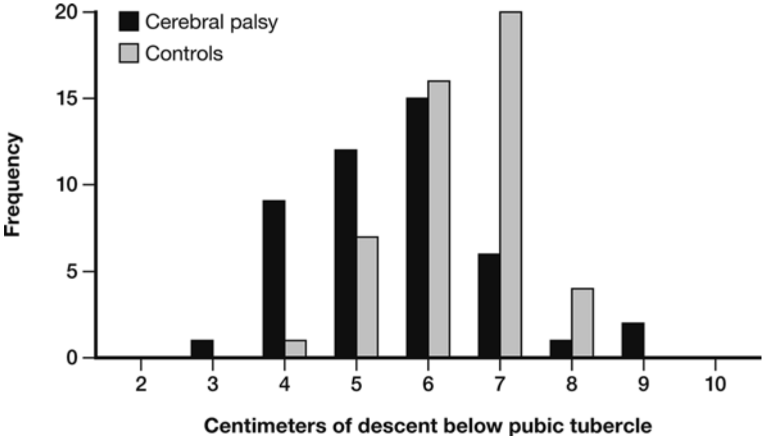

Fig. 5.6 Testicular position in infants less than 30 months of age. The position of the middle of the testis in centimetres below the pubic tubercle is recorded against the frequency for infants with cerebral palsy versus normal infants (Reproduced with permission from Smith et al. [45])

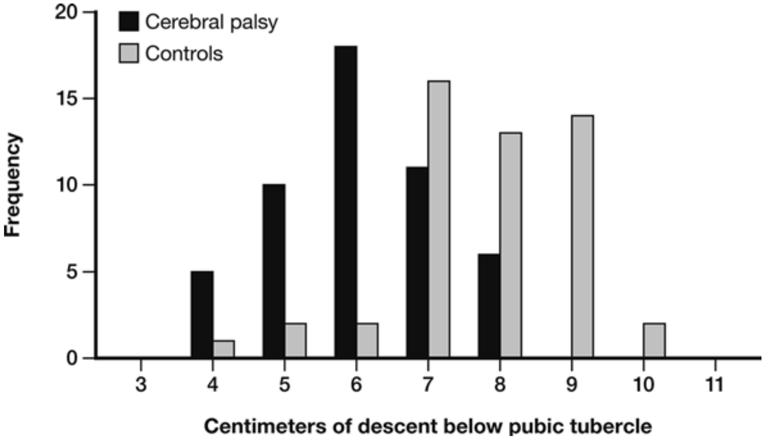

Fig. 5.7 Testicular position in children between 5 and 10 years of age. The position of the middle of the testis in centimetres below the pubic tubercle is plotted against the frequency for normal boys versus boys with cerebral palsy (Reproduced with permission from Smith et al. [45])

To check this possibility, boys with an unequivocal diagnosis of cerebral palsy were compared with age-matched controls selected from within the general inpatient population [45].

In infants with cerebral palsy, the midpoints of the testes were on average 5.2 ± 1.2 cm (mean ± S.D.) below the pubic tubercle compared with 6.1 ± 0.8 cm in the children in the age-matched control group (Fig. 5.6). In 5- to 10-year-old children with cerebral palsy, the testes remained in a similar position, 5.6 ± 1.4 cm, whereas in the children in the age-matched control group, the testes were significantly lower (7.3 ± 1.3 cm) (Fig. 5.7). While the testes remained the same distance below the pubis in cerebral palsy, the distance increased significantly in normal children. These data suggest that there may be no prenatal interference with descent in cerebral palsy but rather the cremaster muscle, which may become spastic during childhood, caused secondary ascent of the testis and/or prevents elongation of the spermatic cord with growth. This hypothesis suggests that the incidence of acquired cryptorchidism would increase during childhood as spasticity increases. These data would fit with the observations of Rundle et al. [38] and Cortada and Kousseff [39] that in older children and adults, the apparent incidence of cryptorchidism may reach 50 % [41].

5.9 Testicular–Epididymal Fusion Abnormalities

A number of testicular–epididymal fusion abnormalities have been described [46, 47] (Fig. 5.8). These abnormalities may contribute to the higher rate of infertility seen in adults who had UDT during childhood.

All descriptions of epididymal abnormalities report a high incidence of concomitant cryptorchidism [48–50]. The comparative incidence in boys with normally descended testes is not known for certain but is believed to be low. Abnormalities range from simple epididymal elongation to complete separation of the epididymis and testis [48]. The higher the arrest of testicular descent, the more abnormal the associated ductal system tends to be [51].

Where there is a severe epididymal abnormality or complete separation of the two structures, as is most commonly observed in intra-abdominal or intracanalicular testis, the as yet unresolved question which must be asked is whether it would be appropriate to remove the gonad in this situation, as sperm transport is bound to be

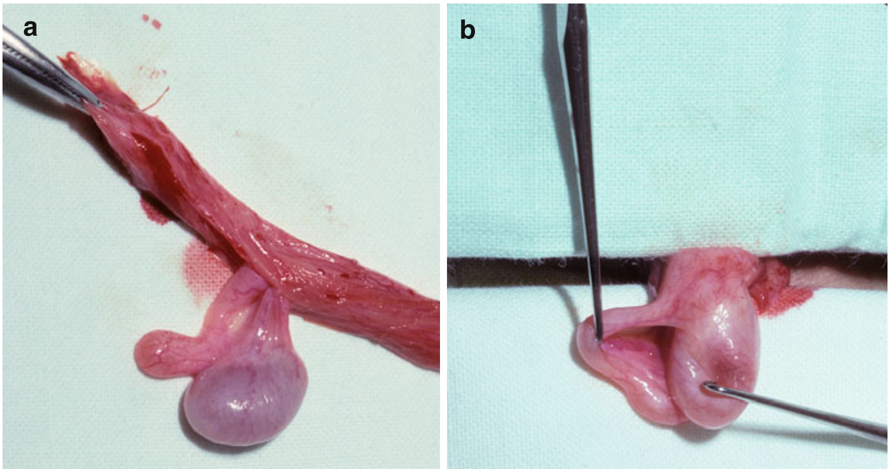

Fig. 5.8 Partial separation of the testis and epididymis as seen at orchidopexy. (**a**) Here the caudal epididymis is detached from the lower pole of the testis, although the rete testis is intact. (**b**) Here the head and tail of the epididymis are attached but the body is detached

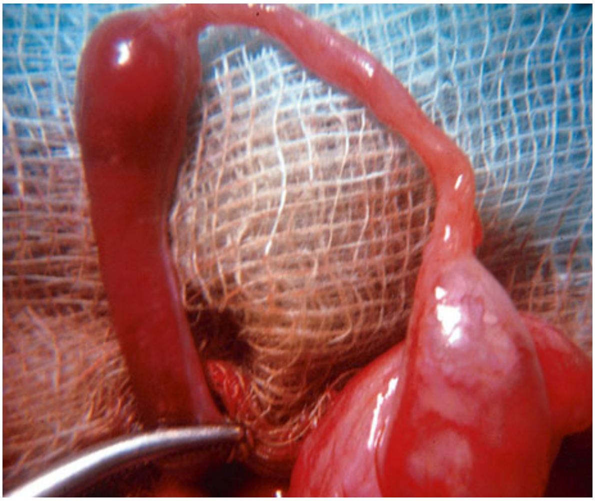

Fig. 5.9 Splenogonadal fusion, in which the left testis is attached by a fibrous cord to splenic tissue (Reproduced with permission from Beasley et al. [52])

affected [53]. Early successful orchidopexy alone may not ensure subsequent fertility despite the presence of normal germ cells [51].

5.10 Rare Fusion Anomalies

On the left side, the testis on rare occasions may be attached to a tongue of splenic tissue, which may or may not be connected to the spleen itself (Fig. 5.9). An hypothesis is proposed that in cases of splenogonadal fusion, an abnormally developed diaphragmatic ligament is colonised by splenic cells, possibly because of an abnormal proximity to the splenic anlage, with the resulting abnormal ligament persisting as the splenic cord and thus resulting in cryptorchidism. This must be related to an abnormal midline development in the third to fourth week of gestation [54].

Conclusion

This chapter describes a number of different abnormalities and syndromes in which the incidence of cryptorchidism is significantly higher than in the general population. However, when understanding the pathogenic relationship, each abnormality and syndrome may give some information to explain different aspects of testicular maldescent.

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The Postnatal Effects of Cryptorchidism

6

6.1 A Primary Anomaly or Secondary Effects?

Since John Hunter first took a scientific interest in undescended testis (UDT) and the mechanism of testicular descent, it has been under debate as to what extent the testis is primarily abnormal leading to maldescent, or alternatively, the testis is undescended and becomes secondarily abnormal. Because UDT comprises a heterogeneous group of conditions, including some which have known primary abnormalities of the testes, it is not always easy to separate primary causes from secondary effects. A growing body of evidence suggests that many of the abnormalities seen postnatally in cryptorchidism are secondary, although, probably in some cases, especially in bilateral UDT, primary abnormalities in the hypothalamic–pituitary–gonadal axis lead to inadequate hormone stimulation of the testes and subsequent maldescent and germ cell deterioration. In this chapter we will discuss the documented abnormalities seen postnatally in cryptorchidism, trying to discriminate between those that are more likely to be secondary abnormalities and those that might be primary in origin.

6.1.1 The Effect of Temperature

The secondary effects seen in UDT are thought to be caused by the increased temperature of the UDT compared with its scrotal counterpart. The scrotal testis resides in a specialised low-temperature environment with heat-exchange mechanisms in the pampiniform plexus, pigmentation of the scrotal skin, absence of subcutaneous fat, and regulation by temperature-sensitive muscles, i.e. the cremaster and dartos muscles (Fig. 6.1) [1]. In the human, the scrotal testis is at 33 °C compared with an inguinal testis which is at approximately 35 °C and the intra-abdominal testis at 37 °C [1]. On an evolutionary time scale, the testis has descended into this specialised external, low-temperature environment for advantages in sperm storage, particularly in the epididymis [2, 3]. The 120 million years which has elapsed since the

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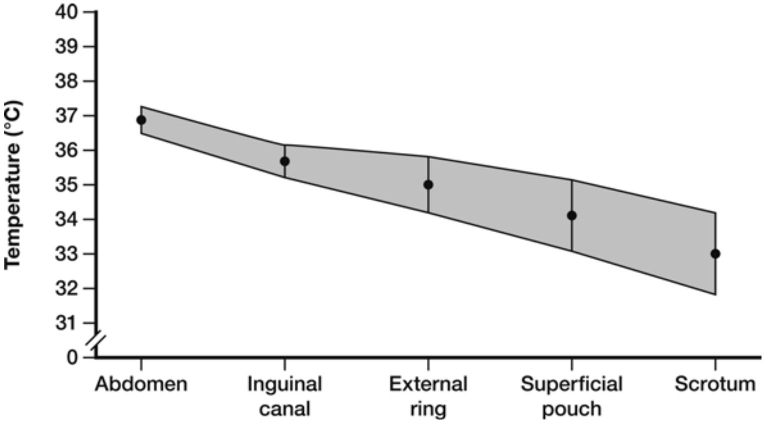

Fig. 6.1 The temperature (mean + SD) of the various sites where the testis may be found, showing that the scrotum is a specialised low-temperature environment (Adapted and redrawn from Sutthoff-Lorey and Wang [1])

testis first descended in primitive mammals has allowed ample time for adaptation of the physiological mechanism within the postnatal testis to this special environment. It is not surprising, therefore, that in UDT the secondary increase in the ambient temperature of the testis leads to progressive dysfunction. Most enzymes and cellular mechanisms within the testes appear to be well adapted to this lower-than-normal body temperature [4]. Significant derangement of germ cell development in cryptorchid testes begins postnatally, although the changes in testicular physiology that normally occur to adapt to the lower temperature are not known, but it is expected to be in the first few weeks after birth. The abnormally high temperature of the cryptorchid human testis is considered by many authors to be the main or additional cause of this germ cell maldevelopment. Considerable studies have been performed in various animal models showing that heat stress leads to a combination of both indirect and direct effects on the germ cells, causing impaired transformation and maturation as well as affecting apoptosis. This thermal injury is mediated by reactive oxygen species and certain heat-shock proteins, which damage the germ cells as well as Sertoli cells [5–9].

6.2 Endocrine Effects

6.2.1 Hormonal Levels of FSH, LH, and Testosterone in Humans

To understand the potential effects of UDT on hormone levels postnatally, it is important to recognise the latest advances in research in this area, which shows that there is a transient surge in gonadotrophins and androgens at about 2–4 months of age, known as ‘minipuberty’ (Box 6.1).

Box 6.1: Minipuberty

In the first few weeks after birth, the testis is quiescent, in contrast to the hormonal activity in the fetus in response to hCG and fetal pituitary hormones. At about 2 months of age, the hypothalamic–pituitary axis is activated, with a burst of production of the gonadotrophins, FSH, and LH. The infantile Leydig cells respond with brief a burst of testosterone production, causing the blood levels of androgen to be similar to that seen in adolescence for a few months. By 6 months of age androgen levels fall. In this minipuberty (2–4 months of age), there is an increase in Sertoli cell number and production of inhibin-B (inhibin-B has a maximum value around 3 months of age, and the elevated inhibin-B persists for a longer period of time than the elevated FSH, LH, and testosterone, as it remains elevated to 15 months of age and decreases to basal levels during the third year of life). The Sertoli cell production of AMH peaks at about 12 months and then declines, but remains measurable to puberty.

The recognition of minipuberty in infants is relatively recent, and there is little definitive research demonstrating its function. However, there has been speculation about its potential role in gender identity [10] and closure of the patent processus vaginalis (PV) after testicular descent is complete [2, 11].

Relevant to management of UDT, minipuberty has been proposed to regulate gonocyte transformation into spermatogonial stem cells (type A spermatogonia) [12] and is the theoretical basis for recommending gonadotrophin and/or gonadotrophin-releasing hormone analogues to treat impaired germ cell development in infants with UDT. The germ cell response to exogenous activation of the hypothalamic–pituitary gonadal axis has been interpreted as showing a role for androgen in early germ cell development [9, 13]. However, recent work from our own laboratory and that of others shows no direct role of androgens, as early germ cell development, including transformation of gonocytes into spermatogonial stem cells, was not perturbed by lack of androgen receptors in both children and a mouse model of complete androgen resistance [14].

With the recognition that gonocyte transformation occurs at minipuberty, but is not controlled by androgen directly, current research is focused on the possibility that gonadotrophins may act via the Sertoli cells and release of local signalling molecules, such as activin or other factors belonging to the transforming growth factor beta (TGFbeta) family.

Early attempts to measure LH and FSH in humans with UDT [15] showed that LH serum levels were normal in cryptorchid boys, whereas some had elevated FSH levels. The authors speculated that elevated FSH may correlate with deranged testicular function, while elevated LH occurred only when the gonad was absent. Kock and Rahlf [16] performed LHRH stimulation tests on boys with UDT and compared them with a control group that had undergone previous surgery for cryptorchidism. They found about 80 % of the prepubertal boys had low or normal basal levels of

LH, while 20 % had elevated levels. They concluded that this variable response to gonadotrophin indicated a heterogeneous group of patients. The results of these studies have been confirmed by Thorup et al. [17, 18] who found that in approximately 25 % of both bilateral and unilateral cryptorchid cases FSH was increased and also in approximately 25 % of bilateral and unilateral cryptorchid cases LH was increased, although the same patients had not necessarily both gonadotrophins elevated (Fig. 6.2).

Gendrel et al. [21] have examined the plasma gonadotrophin and testosterone levels in infants with UDT. In approximately half these infants, the testes descended spontaneously between 2 and 4 months. In those children in which the testes remained undescended, the postnatal rise in the plasma LH level and testosterone concentrations were significantly lower than normal, and there was a correlation between the plasma LH and testosterone levels. They postulated an abnormality in LH secretion as the cause for cryptorchidism leading to a deficient postnatal surge of testosterone. Their documented androgen deficiency postnatally is probably a primary abnormality only in a fraction of boys with UDT. Toppari et al. [22] advocate in their review in 2007 that cryptorchid boys have normal testosterone levels with slightly but significantly elevated LH levels as compared to healthy boys. This high gonadotrophin drive may compensate for mild Leydig cell dysfunction in cryptorchidism. This is in accordance with our findings (Fig. 6.2). Another account of steroidogenesis in normal and cryptorchid boys is provided by Jockenhovel and Swerdloff [23].

Van Vliet et al. [24] investigated 40 prepubertal boys with LHRH stimulation tests. They found an increase in basal FSH levels and an increase in FSH response to LHRH in both unilateral and bilaterally cryptorchid boys. The FSH receptor levels per testis were lower in the UDT than in the normally descended testis [25]. The level of LH receptors was also found to be significantly inhibited.

In a study by Thorup et al. [26], bilaterally cryptorchid boys aged 9 months to 3.7 years with normal or severely decreased testicular germ cell number had a gonadotrophin-releasing hormone (GnRH) stimulation test carried out with 100 µg Suprefact ® and blood samples for LH and FSH at t:0 and t:30 min. Most patients had normal basic hormonal values and a normal response, but among the patients with severely decreased testicular germ cell number, more than 50 % had elevated FSH, indicating hypergonadotrophic hypogonadism. However, 23 % of the patients in that study had an insufficient rise in LH and/or FSH indicating a transient hypothalamic–pituitary–gonadal hypofunction. In a few patients there was a different response in FSH compared with LH secretion after GnRH stimulation.

Baker et al. [27] looked at premature infants born with a mean gestational age of 30 weeks. Although some testes descended spontaneously postnatally, there was a persisting high incidence (up to 19 %) of UDT at 18 months of age. The normal testosterone surge in the second postnatal month failed to develop in these premature babies with subsequently proven cryptorchidism. In addition, these premature babies failed to show an immediate postnatal testosterone peak which is normally seen in association with residual hCG in the neonatal circulation. They concluded that inadequate stimulation of testosterone by hCG in utero may contribute to the

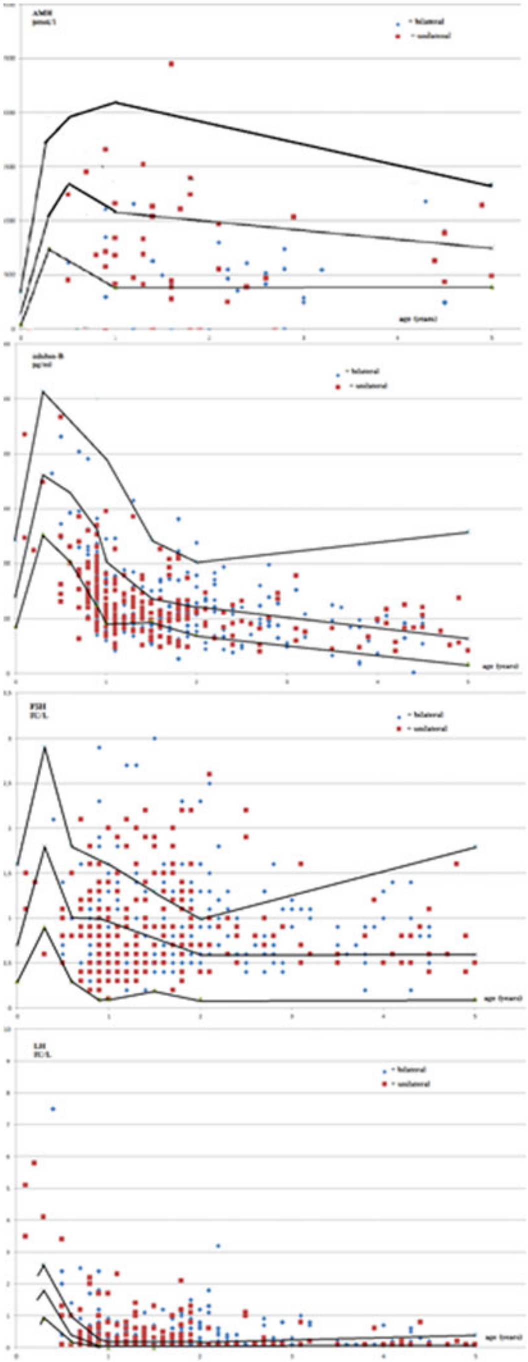

Fig. 6.2 The serum values of FSH, LH, inhibin-B, and AMH from boys with unilateral or bilateral cryptorchidism related to normal median and range (Modified from references Baker et al. [19] and Cortes et al. [20])

pathogenesis of UDT in this special group of premature babies. The antenatal main source of hCG is production by the placenta. This is in accordance with the findings that insufficient placental function leads to higher incidence of congenital cryptorchidism (see Chap. 4).

In a detailed study of androgen levels in infancy, Job et al. [28] found significantly decreased plasma testosterone levels and LH levels from 1 to 4 months of age. After 4 months of age, the normal LH and testosterone levels were very low, and no differences could be documented between cryptorchid infants and normal children. They found antibodies against gonadotrophin-producing cells in the pituitary on immunofluorescence in half the infants with UDT and speculated that maternal autoantibodies may be responsible for partial gonadotrophin deficiency in the perinatal period, leading to UDT in the male offspring. In these very small infants, FSH basal levels and levels in response to LHRH were found to be within the normal range.

Indeed the variable gonadotrophin response indicates the heterogeneity of cryptorchid patients. Due to the low normal range of both gonadotrophin serum levels in childhood, insufficiency is most easily seen in the minipuberty. In contrast, increased serum levels can be demonstrated at any time. When all patients are pooled together, the slightly elevated gonadotrophins compared to normal are the overall result (Fig. 6.2).

6.2.2 Inhibin-B

Inhibin-B is a hormone produced by Sertoli cells and consists of an α-subunit and a βB-subunit. In the prepubertal human testes, both α- and βB-subunits of inhibin-B are co-localised in Sertoli cells, whereas in adult human testes, the two subunits constituting inhibin-B are expressed by different cell types [29–32]. The Sertoli cells express receptors for FSH [25, 33].

As described in the previous section, the hypothalamic–pituitary–gonadal hormone axis is transiently activated during the first months of life resulting in increased serum levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), and testosterone. Inhibin-B is similarly elevated [29]. The elevated inhibin-B persists for a longer period of time than the elevated FSH, LH, and testosterone, as it remains elevated to 15 months of age and decreases to basal level during the third year of life [29, 34]. During the prepubertal period, inhibin-B is secreted in detectable amounts, while FSH, LH, and testosterone are low (Fig. 6.2) [35]. The rise in inhibin- B may reflect the increase in the number of Sertoli cells that occurs during the first 3 months of life [19, 36]. Zivkovic and Hadziselimovic [37] also found that the number of Sertoli cells increased with the hormonal surge. But in cryptorchid patients, the number of Sertoli cells was diminished compared to the normal testis. During puberty inhibin-B becomes inverted to FSH [31, 34, 35].

Inhibin-B may reflect the histological state of seminiferous tubules. Basal inhibin-B levels have been shown to predict the human chorionic gonadotrophin-stimulated testosterone response, suggesting that the presence of testicular tissue can be determined by a single inhibin-B measurement [38, 39]. Studies of inhibin-B in cryptorchid boys have yielded mixed results, reporting normal values [31, 32, 38, 40, 41] or decreased values [42]. In studies by Thorup et al. [17, 18] inhibin-B was decreased in 24 % of bilateral cryptorchid and 16 % of unilateral cryptorchid patients (Fig. 6.2). Decreased inhibin-B was primarily identified among patients with a decreased number of spermatogonia and gonocytes. Consequently, a decreased inhibin-B predicts a high risk of later infertility.

As previously mentioned some studies reported inhibin-B in cryptorchid boys [31, 32, 38, 40, 41]. However, when analysing these studies in detail, it appears that in three of these studies [32, 37, 39], decreased inhibin-B values were found in some bilateral cryptorchid patients, as in the studies by Thorup et al. [17, 43]. Kubini et al. [37] reported that patients with intra-abdominal testes had normal values of inhibin-B, but from the paper it appears that 20 % (1/5) of these five patients had decreased inhibin-B. Christiansen et al. [32] reported decreased inhibin-B values in some bilateral cryptorchid boys with at least one nonpalpable testis. These patients were about 7 years old. Irkilata et al. [39] found low values of inhibin-B in some patients with bilateral cryptorchidism, as 2 patients with bilateral nonpalpable testes had decreased inhibin-B values, whereas 13 patients with unilateral palpable testis had normal inhibin-B values. In the study by Thorup et al. [18], 16 % of 50 unilateral cryptorchid patients had inhibin-B serum levels below normal range. In a study by Kollin et al. [44] of pre- and postoperative inhibin-B serum values in 58 and 62 one-year-old unilateral cryptorchid boys, the inhibin-B serum level seemed higher in the postoperative group (168 ± 88.4 pg/ml) compared to the preoperative group (160 ± 66.5 pg/ml). Interestingly, Thorup et al. [18] found a high proportion of testes with impaired germ cell number among those boys who had an absolute increment of inhibin-B serum values after surgery in unilateral cryptorchid testes. So the serum inhibin-B increment may actually reflect an improvement of the histological state of the seminiferous tubules of the UDT among some children after surgery. These findings are indirectly supported by other studies [44, 45]. One study showed that the serum level of inhibin-B correlated positively to testicular volume in newborn boys [45]. This was confirmed by Kollin et al. [44], who found that boys with unilateral cryptorchid testes with high levels of inhibin-B at 6 months and 4 years also had

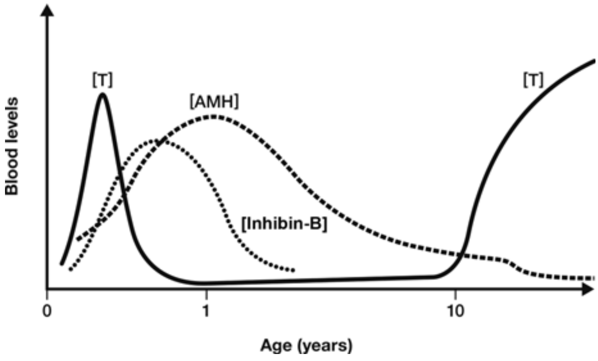

Fig. 6.3 Schema of AMH serum levels at different ages. Note the peak of secretion from 4 to 12 months (Redrawn from Baker et al. [19]). The levels of testosterone and inhibin-B are shown on the same time scale

bigger testes at 4 years than boys with low levels of inhibin-B. Furthermore, a good correlation was found between the number of germ and Sertoli cells and testicular volume at time of operation with biopsy [44]. Interestingly, only 10 % of the unilateral cryptorchid patients in the study by Thorup et al. [18] had a serum level of inhibin-B above the normal median (50 percentile) preoperatively compared to 40 % postoperatively. So there was a trend towards a more normal distribution of serum levels of inhibin-B postoperatively. Based on these studies [18, 44, 45], there is now good evidence that in unilateral cryptorchidism, an increment of the serum level of inhibin-B postoperatively may indicate testicular growth due to improvement of the histological state of seminiferous tubules. The patients that followed the normal physiological percentile decline of serum inhibin-B level seen in this age group seemed to have better germ cell number at operation, so therefore testicular growth due to further improvement of the histological state of seminiferous tubules would probably not be expected to the same degree. Also in bilateral cryptorchid cases, a postoperative increase of inhibin-B serum levels has been shown in 20 % of patients [17]. In bilateral cryptorchid patients, low serum levels of inhibin-B and impaired germ cell number in testicular biopsies are in some cases reflected by increased FSH, indicating hypergonadotrophic hypogonadism, and in some cases FSH remains normal, indicating a transient hypothalamic–pituitary–gonadal hypofunction [17].

6.2.3 Anti-Müllerian Hormone (AMH)

Studies in Melbourne utilising an enzyme immunoassay for AMH (previously called Müllerian-inhibiting substance or MIS) show a peak of secretion between 4 and 12 months of age [19] (Fig. 6.3). AMH peak levels are therefore occurring after the postnatal surge of androgen secretion between 1 and 4 months of age. Lee et al. [46] also found normal male peak levels in the second half of the first year of life. This was later partly confirmed by Askeglaede et al. in [47], who found slightly higher median serum levels of AMH in 1-year-old normal boys compared to serum levels of AMH in 3-month-old boys. When levels of AMH in normal children were compared with those undergoing orchidopexy, a deficient surge of AMH secretion between 4 and 12 months of age was documented (Fig. 6.4) [48]. In later years of childhood, there was a measurable but not always statistically significant inhibition in AMH levels in boys with UDT. Importantly, in the first 3 months of life, no deficiency of AMH secretion could be documented in the small number of cases measured. This would be consistent with the later depression in AMH secretion being a secondary rather than a primary abnormality. In a material of 156 boys with cryptorchidism (age 1 day–20 years), the percentage of subjects with normal, low, or absent AMH values was similar between boys with unilateral or bilateral cryptorchidism. Overall, 46.8 % of AMH values were normal, whereas 24.4 % were low (below the male range for age), and 28.8 % were undetectable. Thus, the associated findings of microphallus or hypospadias did not significantly affect serum AMH concentrations in boys with cryptorchidism. Eighty boys had cryptorchid testes that

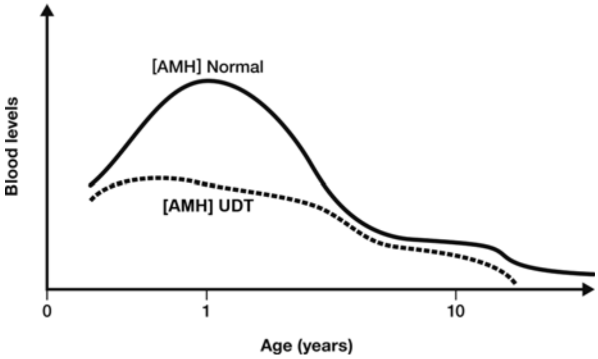

Fig. 6.4 Schema in boys with undescended testes and paired, age-matched controls. Note the lack of a peak of secretion at 4–12 months in boys with undescended testes (Redrawn from Yamanaka et al. [48])

were distinguishable as palpable (inguinal or retractile; $n=46$) or nonpalpable ($n=34$). AMH was normal for age in 65 % of those with palpable testes and 25 % of those with nonpalpable testes. Boys with nonpalpable testes had the highest percentage (50 %) of undetectable AMH values [49]. AMH is secreted by the Sertoli cells, and Cortes et al. (2015) [20] found a good correlation between serum levels of AMH and inhibin-B in cryptorchid boys older than 1 year but not in boys younger than 1 year. This finding is in accordance with the aforementioned results from the studies by the Melbourne group that the peak of AMH secretion is delayed and not so impressive compared to the peak of inhibin-B secretion, although both hormones are produced by the Sertoli cells.

In cryptorchid testes both serum AMH and inhibin-B are positively correlated to the serum level of LH, but this is not the case in relation to FSH. Different pathways of feedback mechanisms may explain these findings (Cortes et al. 2015 [20]).

6.3 Morphological Effects

6.3.1 Human Studies

It was once thought that morphological abnormalities within the UDT, i.e. germinal cell deficiency, were congenital [50]. However, in several studies it has been observed that the testicular morphology often is more normal initially and then becomes increasingly abnormal as childhood progresses. The first macroscopic changes are seen in 5–10-year-olds, where the testis may be small and softer than normal. Histologically, they show signs of dysplasia. In minipuberty the first thing happening is an increase of Sertoli cell number. In cryptorchid testes, however, the Sertoli cell number is diminished compared to normal (see Sect. 6.2.2). In 1974, Mengel et al. [51] reported on a large histological study of 752 testicular biopsy specimens from children between 2 months and 15 years of age. They counted the number of spermatogonia observed in 50 tubules and measured the diameter of the tubules and were unable to identify abnormalities in the first or second year of life. By contrast, in the third year of life, they found a significant fall in the number of the spermatogonia per tubule and a lack of the normal enlargement of the tubules. Similar but less severe abnormalities were observed in the unilaterally descended testes at a later age. They concluded that to prevent this apparently secondary effect on testicular morphology, orchidopexy should be performed before the second birthday. Cortes et al. [20] found that at birth cryptorchid patients harbour germ cells in the testes, but in reduced number compared to normal. From about 15 months of age, germ cells may be lacking (Fig. 6.5). The higher the age at orchidopexy, the higher was the risk of finding no germ cells on testicular biopsy tissue. Hadziselimovic et al. [53] performed electron microscopic studies on testicular biopsies collected at orchidopexy. They found no ultrastructural abnormalities in the tubules before the first birthday, although there were early abnormalities in the Leydig cells. Hadziselimovic et al. published detailed accounts of their histological studies in the mid-1980s. They found that development of the Leydig cells between 2 and 6 months was impaired in UDT, whereas the Sertoli cells and germ cells appeared normal. Around 6 months of age (just after 'minipuberty'), the normal transformation of gonocytes into spermatogonia was completed, and the number of germ cells begins to diminish significantly, even in normal boys. In Box 6.2, we summarise the current understanding about early germ cell development in normal children and animal models, so that the changes seen in UDT can be put in perspective (Fig. 6.6).

The severity of germ cell deficiency in cryptorchid testes is directly related to the position of the testis, with higher or intra-abdominal testes being more severely abnormal than testes located just outside the scrotum [57, 58]. Hadziselimovic concluded that germ cell deficiency in UDT is a secondary abnormality. In UDT examined by biopsy, only one infant in 92 younger than 12 months of age lacked all germ

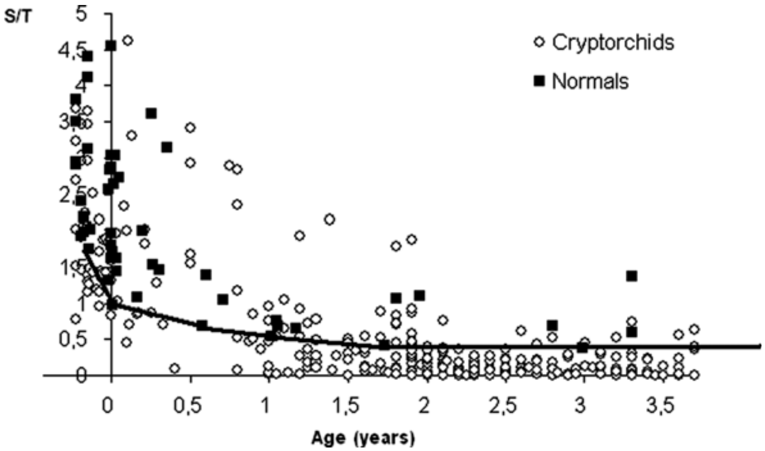

Fig. 6.5 The number of spermatogonia, and gonocytes if any, per tubular cross section (S/T) in 35 human cryptorchid fetuses and in 261 boys who underwent surgery for cryptorchidism <4 years of age. Furthermore, S/T in 22 normal human fetuses and 25 normal boys who died <4 years of age. The *solid line* indicates the lowest normal S/T

cells, and 70 % of the testicular biopsies examined had a normal number of germ cells [13]. Saito and Kumamoto [57] found decreased numbers of germ cells in about 30 % of the contralateral testes in unilateral cryptorchidism. Using sophisticated histological techniques with plastic embedding of the testicular biopsies, Huff et al. [9] studied 232 biopsies from unilateral cryptorchid testes and 195 contralateral descended testes. Decreased numbers of germ cells were documented from the first year of life. The transformation of gonocytes to adult dark spermatogonia, which normally is complete around 6 months of age, was delayed or defective. In addition, the transformation of adult dark spermatogonia to primary spermatocytes, which normally commences at about 3 years of age and is complete by about 4–5 years, was also delayed or absent. They concluded that UDT showed features of transient hypogonadotropic hypogonadism as the cause of the increased incidence of infertility in these patients.

In studies with immunohistochemical staining methods of testicular biopsies from cryptorchid testes, a delayed maturation of gonocytes into spermatogonia is clearly demonstrated [59]. In 1993 Jorgensen et al. [60] found that in gonads from normal boys PLAP-positive germ cells were seen in 41 % (13/32) up to 1 year of age but in 0 % (0/169) from 1.1 to 14.7 years. Honecker et al. [61] found PLAP-,

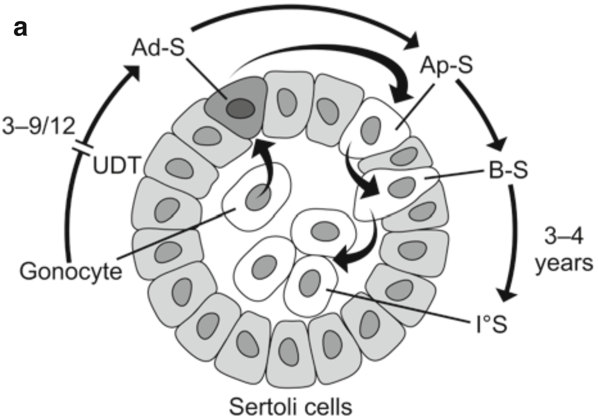

Fig. 6.6 (**a**) Germ cell development shown in the tubule. The gonocyte (*white*) begins in the centre of the cord. At 3–9 months, it migrates between Sertoli cells (*grey*) to reach the basement membrane, where it differentiates into an Ad-S (*dark grey*), which sits on the membrane and has dense cytoplasm and a prominent nucleolus. The Ad-S is thought to be the stem cell for subsequent development into adult-pale spermatogonia (Ap-S; *white*), intermediate spermatogonia, type B spermatogonia (B-S; *white*), and then primary spermatocytes (1˚S; *white*) at 3–4 years. Cryptorchidism (UDT) blocks the first step (colours of germ cells refer to their appearance in standard histological sections). (**b**) Immunofluorescent histochemistry of testis in androgen-receptor knockout (*ARKO*) and wild-type (*WT*) mice at postnatal days 0, 2, 4, and 8, for AMH (*green*, marks Sertoli cells) and MVH (*red*, marks germ cells), *blue*=DAPI, bar = 10 um. (**c**) Immunofluorescent histochemistry of testis in ARKO and WT mice for Ki67 (*red*, marks proliferating cells) and MVH (*green*, marks germ cells), *blue*=DAPI, bar-10 um (Reproduced with permission from Li et al. [54])

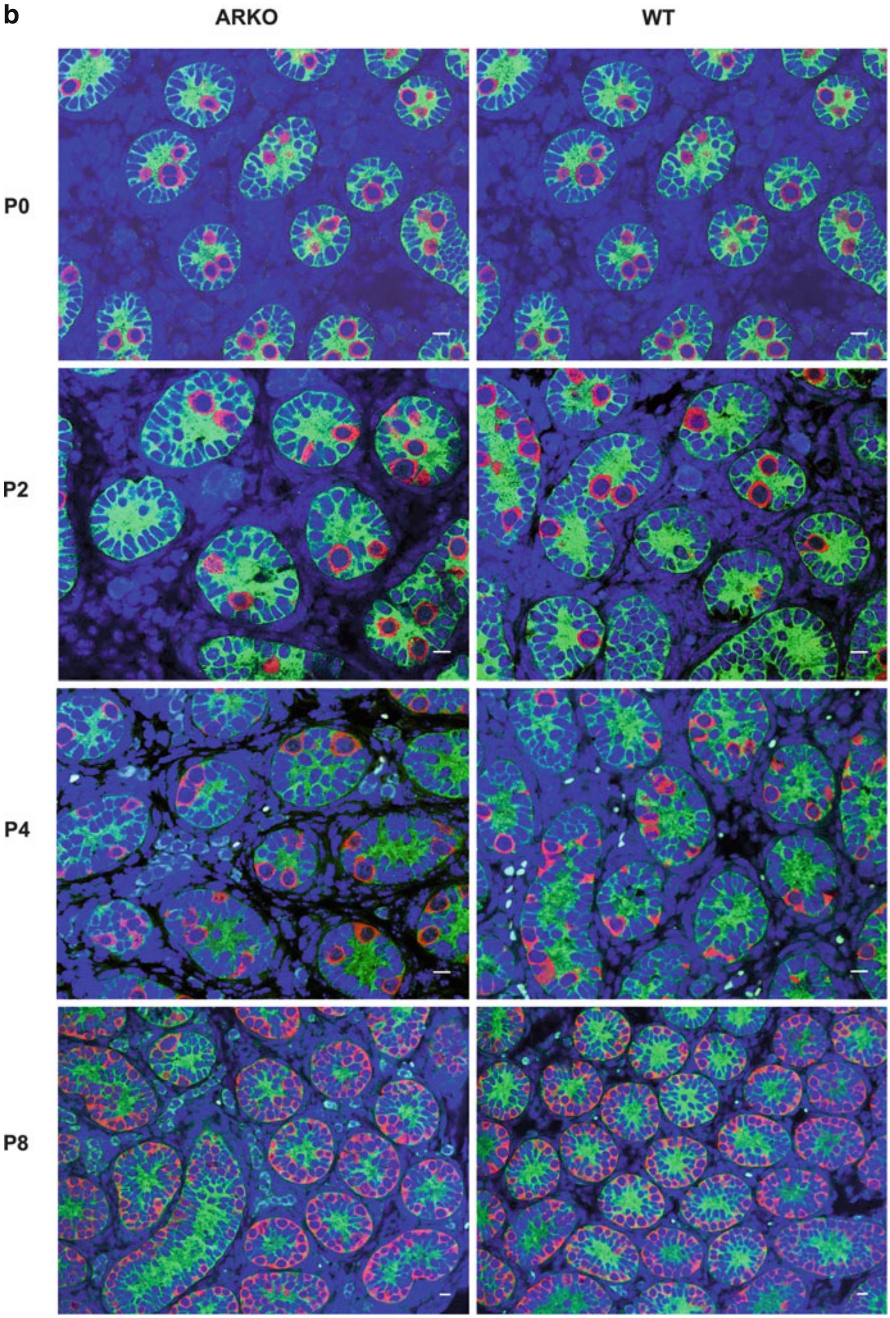

Fig. 6.6 (continued)

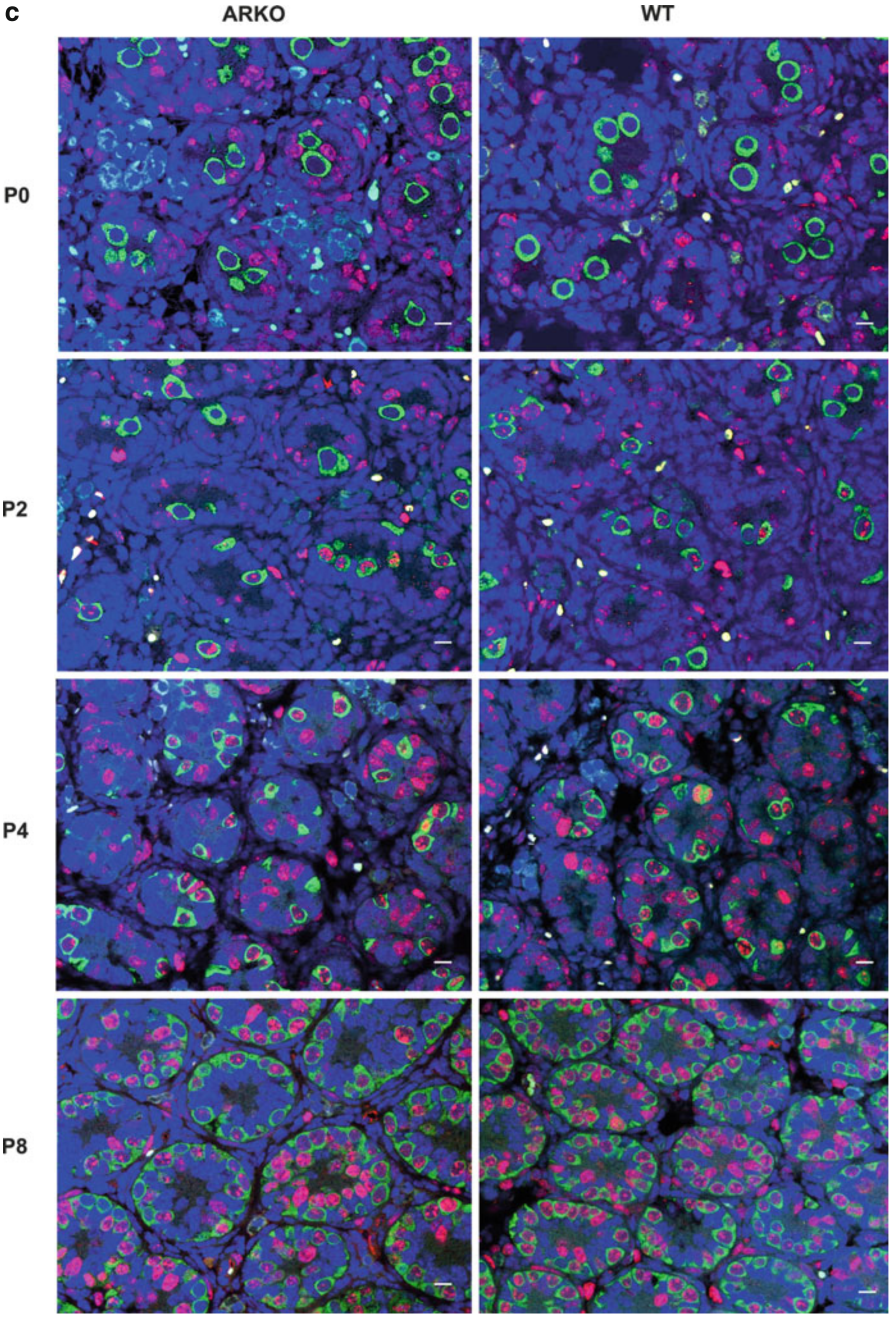

Fig. 6.6 (continued)

Box 6.2: Normal Germ Cell Development in the Postnatal Testis

At about 5–6 weeks' gestation in the human fetus, the primitive germ cells migrate from the yolk sac stalk and colonise the developing gonads in the urogenital ridges [55]. Sexual differentiation begins at 7–8 weeks' gestation, and the ambisexual gonad differentiates into a testis or ovary. With testicular development in the male, the primitive Sertoli cells form into cords or tubules, surrounding the germ cells and separating them from the interstitial space that contains the Leydig cells. At birth the primitive germ cells, known as neonatal gonocytes, are located in the centre of the seminiferous tubules.

From about 3 months of age, the neonatal gonocytes begin to migrate between the Sertoli cells to reach the basement membrane of the tubule, where they transform into type A spermatogonia, which are now thought to be the stem cells for spermatogenesis after puberty [56]. Gonocytes that fail to transform normally undergo apoptosis, clearing the tubule of any totipotential germ cell that might lead to cancer later in life. By 9–20 months of age, the neonatal gonocytes have completely disappeared, and the type A spermatogonia (at 1–2 years) begin to differentiate into type B spermatoginia, with further development into primary spermatocytes at 3–4 years of age. The primary spermatocytes are located in the centre of the tubules similar to where the gonocytes were found at birth. The primary spermatocytes appear to be quiescent until the onset of puberty.

For many years the appearance of primitive germ cells in the centre of the tubules from birth and throughout the prepubertal years was taken as evidence that no important changes were occurring in the germ cells between birth and puberty. In retrospect this was because the neonatal gonocyte looked similar to the primary spermatocyte, except in size, with the latter cell much smaller. Now we recognise that the most important stage in prepubertal germ cell development is the migration of the neonatal gonocyte to the basement membrane and its transformation into a type A spermatogonium, now recognised as the spermatogenic stem cell.

In most boys with UDT, the number of gonocytes in the tubules is normal or close to it, but transformation into type A spermatogonia is perturbed. In addition, the normal apoptosis of untransformed gonocytes is also perturbed, leading to gonocytes persisting in the UDT at 2 years of age, a time when they should have disappeared. After 1 year of age persisting maldescent leads to cell death of germ cells, including spermatogonial stem cells with serious implications for fertility.

The regulation of gonocyte transformation into stem cells for spermatogenesis is not fully understood, but is highly likely to be a result of the transient hormonal surge at 2–6 months, now known as 'minipuberty' (see Box 6.1).

Oct3/4-, and C-kit-positive germ cells in gonads of normal neonatal boys. In cryptorchid testes, delayed germ cell maturation is demonstrated by the presence of Oct3/4-positive germ cells up to 1 2/3 years of age and PLAP- and C-kit-positive gonocytes until much later in childhood [59]. Also another study demonstrated immunohistochemically that germ cell development in cryptorchid testes was deranged significantly postnatally as the process of maturation was clearly delayed [62] (Fig. 6.7). The first step to fail is transformation of gonocytes into type A spermatogonia, which is delayed or interrupted. Evidence for this disruption is found in the persistence of large numbers of gonocytes in the spermatic cords well beyond 6 months of age and a decreased number of type A spermatogonia [9, 63]. After the

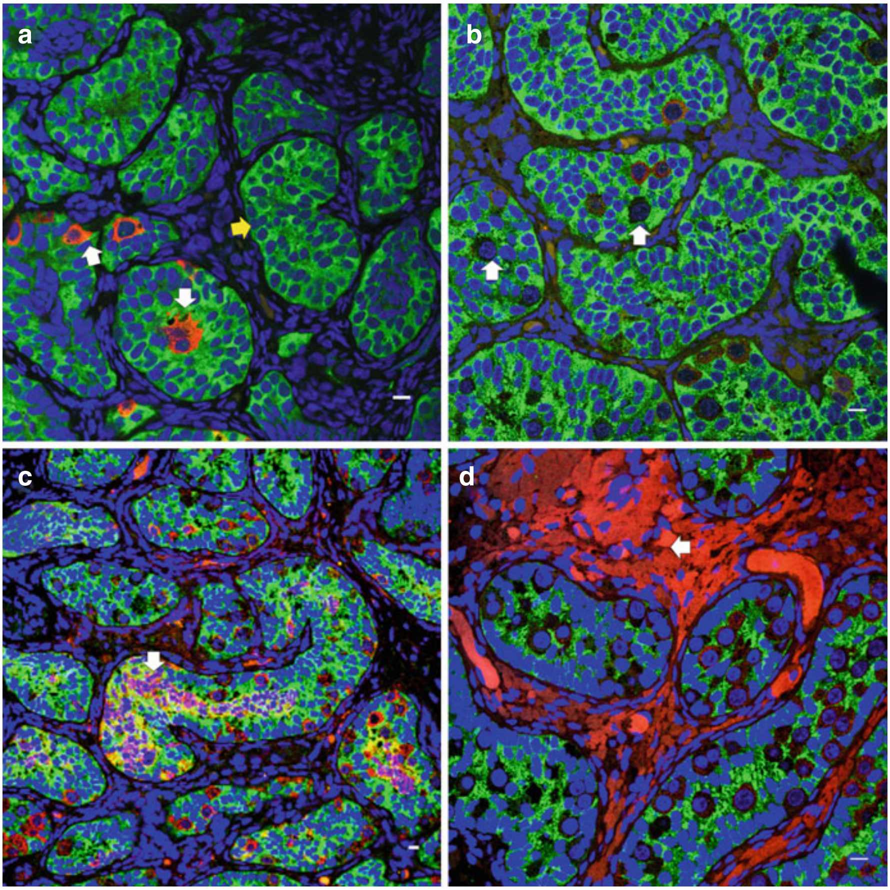

Fig. 6.7 Testicular biopsies at orchidopexy co-immune-stained for AMH (*green*) and MVH (*red*). (**a**) Germ cells (*red*) were migrating towards the basement membrane with protrusions (*white arrow*) and 'empty' tubules without germ cells (*yellow arrow*); (**b**) both MVH+ and MVH-cells (*arrow*) were present in the testicular tubules; (**c**) tubules centrally filled with cells that had small MVH+nuclei (*arrow*); (**d**) fibrosis presented between the tubules (*arrow*). Bar = 10 um (Reproduced with permission from Li et al. [62])

first year, the number of spermatogonia decreases, while those that remain are gonocytes with bizarre nuclei [64]. By 3–4 years of age, the abnormality has become even more obvious, with failure of primary spermatocytes to appear [9]. PLAP is normally predominantly detected in gonocytes [61] so the persistence of PLAP-positive germ cells throughout the rest of childhood, often seen as previously described, is in accordance with the delayed germ cell development seen in cryptorchid testes.

In the adult infertile patient, reduced function of the testicular parenchyma, in the form of spermatogenic arrest and a reduced number of late spermatids, is often seen in previous UDT. Spermatogenic arrest is a morphological pattern where spermatogenesis is blocked and no formation of spermatozoa takes place, but where primary spermatocytes, or more seldom spermatogonia, are the most highly differentiated germ cells [36].

6.3.2 Compensatory Testicular Hypertrophy

A number of other morphological effects of UDT have been reported. Lauren et al. [65] reported compensatory testicular hypertrophy in the contralateral testes in 12 % of children with unilateral UDT.

In childhood the contralateral testis of a unilateral vanished testis may have a 20 % greater volume when there is no ipsilateral viable testis present, compared to the cases where an ipsilateral cryptorchid testis is found [66, 67]. Even greater hypertrophy may be seen peri-pubertally. This hypertrophy of the contralateral testis may be due to the increase in number of Sertoli cells and/or germ cells and is reflected by the trend of increasing serum levels of inhibin-B seen after 1½ years old. If the testis has vanished as a last trimester/perinatal event, it seems reasonable to expect that the first 1–2 years to pass, including the normal minipuberty, before contralateral hypertrophy has developed and normal serum levels of inhibin-B can be demonstrated [68].

6.4 Fertility in the Cryptorchid Testis

Fertility in men with a history of cryptorchidism remains significantly depressed. In the 1950s it was believed that there were no adverse changes in the UDT until after the advent of puberty. This led to the belief that surgical treatment was not necessary until 12–15 years of age [69]. It is now appreciated, as mentioned in the previous section, that germ cell maturation is already abnormal within the first year of life in boys with UDT [13, 36].

Outcomes related to infertility include the paternity rate, semen analysis, measurement of serum LH, FSH and inhibin-B, and testicular size. Probably induced by 'minipuberty', the neonatal gonocytes transform into type A spermatogonia during the first 12 months of age, a step that is now postulated to be crucial for subsequent fertility, as these are the stem cells for spermatogenesis [12]. This step is deranged in UDT, and hence, to avoid this and hypothetically facilitate normal maturation, orchidopexy is currently performed at 6–12 months of age in many centres [70]. Hadziselimovic and Herzog [71] matched histological findings of the testes from 31 patients who had undergone an early orchidopexy with their total number of sperm. If adult dark spermatogonia were present, 17 (94 %) of 18 (95 % CI 72·7–99·9) of the men had a total sperm count of 40×10^6/ejaculate or greater. By contrast, despite successful early surgery, if adult dark spermatogonia were absent, 12 (92 %) of 13 (64·0–99·8) patients had abnormal spermiograms. Thus, the transformation of gonocytes into Ad-spermatogonia is crucial for male fertility. However, if there has been an underlying endocrinopathy causing inadequate maturation of the testis, merely putting the testis into the scrotum will not correct that endocrinopathy.

Histological and hormonal studies presented in the previous sections indicate that approximately 40 % of boys with bilateral cryptorchidism and 10 % of boys with unilateral cryptorchidism have a transient hypothalamic–pituitary–gonadal hypofunction as described by Hadziselimovic and Herzog [17, 18, 72]. Insufficient gonadotrophin stimulation of germ cell maturation will lead to impaired germ cell number in both testes and high risk of later infertility, though the exact mechanism is not yet known. Some studies indicate that the gonadotrophin surge normally may stimulate a non-androgenic testicular factor, such as Sertoli cell-secreted activin or other transforming growth factor beta, to regulate gonocyte transformation into spermatogonia [73–76]. However, several growth factors are involved in the regulation of testicular function. It has been observed that epidermal growth factor, insulin-like growth factor 1 (IGF 1), transforming growth factor beta (TGFB), fibroblast growth factor (FGF), erythropoietin, and insulin are able to influence Leydig cell steroidogenesis by binding to specific plasma membrane receptors [77–79]. Those cryptorchid boys with insufficient gonadotrophin stimulation of germ cell maturation represent the cases that, in respect of fertility potential, might benefit from adjuvant hormonal therapy in relation to orchidopexy (see Chap. 9). In contrast approximately 25 % of boys with bilateral or unilateral cryptorchidism react with increased serum level of FSH and very early deteriorated germ cell numbers (some probably congenital), indicating hypergonadotrophic hypogonadism. The high frequency of these testes found in the inguinal canal or at the level of the external annular ring indicates a congenital malformation [17]. The fertility potential related to hypergonadotrophic hypogonadism is probably dependent on to what extent the germ cell impairment is reversible at time of orchidopexy. It has previously been shown that this group of patients encompasses 55 % of adult infertile men operated for cryptorchidism around 12 years of age [80]. In about one third of boys with cryptorchidism, the high ambient temperature of the cryptorchid testis is probably the major pathogenic factor to inhibit gonocyte transformation and fertility in adulthood and therefore correlated to the age at orchidopexy. There may be overlap between the aforementioned groups with competing factors involved.

6.5 Malignancy

Cryptorchidism is an evidence-based high-risk factor for later testicular malignancy. The relative risk for development of testicular cancer is currently between 3.7 and 7.5 times higher than the background population. The testicular germ cell tumour most commonly associated with cryptorchidism is seminoma. It is generally accepted that the classical seminomas develop from a precursor lesion, intratubular germ cell neoplasia (ITGCN or carcinoma in situ) [81, 82]. It has been hypothesised that understimulation or dysregulation of primordial germ cells or gonocytes during early fetal development is a key event leading to an arrest in germ cell differentiation and hence formation of dormant cells of ITGCN that later in life progress to invasiveness and testicular cancer [83, 84]. This hypothesis regarding cryptorchidism in general is not supported by data [59] as expression of the immunohistochemical testicular neoplasia marker, Oct3/4, is not seen in cryptorchid testes of childhood after the age of 2 years. The expression of Oct3/4 is associated with pluripotency. It is a member of the POU (Pit-1, Oct1/2, UNC-86) family of transcription factors and regulates the transcription of genes favouring self-renewal over differentiation [85]. However, the aforementioned hypothesis that dormant cells of ITGCN in childhood later in life progress to invasiveness may well be the case in DSD, where the germ cell physiology is deranged by the underlying genetic anomaly. By contrast, this seems less plausible generally in cryptorchidism if the maldescent is caused by extraneous mechanical defects or gonadotrophin insufficiency. In cryptorchidism, therefore, the ITGCN may arise from the neonatal gonocytes, which are abnormally abundant (which may be secondary to disturbed apoptosis of gonocytes that have not transformed into spermatogonial stem cells). The gonocyte has pluripotent stem cell properties, which if it persists until after puberty, with or without mutation, may develop into the subsequent cancer [5]. As described in Sect. 6.3.1, we hypothesise that significantly deranged germ cell development in cryptorchid testes begins postnatally. Though insufficient gonadotrophin stimulation may be of importance in some of the boys [43, 63], the abnormally high temperature of the cryptorchid human testis is, as described in Sect. 6.1.1, considered to be the main or additional cause of this germ cell maldevelopment in most cases. The thermal injury mediated by reactive oxygen species and certain heat-shock proteins damage the germ cells as well as Sertoli cells. When further exposure of additional risk factors occurs, supplementary to the heat stress mechanism, this may influence germ cell development as previously described and dramatic effects may be noticed. An increased number of germ cells positive for testicular immunohistochemical markers such as Oct3/4 were seen in testes from second trimester fetuses with chromosomal abnormalities, i.e. trisomy 21 and 18 [61]. These findings are in line with other reports and support the model that chromosomal abnormalities can interfere with normal germ cell maturation [61, 86–88]. As already mentioned disorders of sex development (DSD) and/or the presence of abnormal external genitalia may lead to an increased risk of prepubertal diagnosis of ITGCN [5, 86]. However, also other syndromes associated with cryptorchidism (such as Prader–Willi) and treatment with growth hormones may interfere with early germ cell maturation and act as additional ITGCN risk factors and lead to increased risk of testicular neoplasia in childhood [59, 89, 90].

It is well known that intra-abdominal testes have an especially high risk of developing ITGCN or cancer [36]. One may speculate whether the intra-abdominal position enhances the heat stress mechanism compared to the more distally placed UDT. In cases when the heat stress, as the only factor, may be responsible for development of germ cell neoplasia, it is possibly a long-term effect. This also fits well with the clear evidence from several studies that early orchidopexy may decrease the risk of testicular cancer (see Chap. 10).

Giwercman et al. [91] followed up 500 adult young men who had been admitted consecutively to a group of Danish hospitals with a previous diagnosis of testicular maldescent. Three hundred of these men consented to testicular biopsies where ITGCN was diagnosed in five patients (1.7 %). This is a much higher prevalence of ITGCN than what can be seen in cryptorchid testes during childhood. In a review of 6 studies on 2800 prepubertal testicular biopsies from cryptorchid testes, ITGCN was found in 0.36 % [36]. These findings support also the hypothesis that generally in cryptorchidism ITGCN and later invasive testicular cancer develop over time.

Conclusion

The undescended testis may be morphologically normal or abnormal at time of birth. In some of the cases insufficient gonadotrophin stimulation may lead to impaired number of Sertoli cells and lack of germ cell maturation. As a consequence the Sertoli cell secretion of inhibin-B and AMH will be lower than normal. In most cases the high temperature will lead to further deterioration of the germinative epithelium. Caused by the feedback mechanism, the hypothalamic–pituitary axis, the gonadotrophins may increase. The dysplasia of testicular tissue leads to increased risk of infertility and malignant degeneration.

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Diagnosis of Undescended Testis

7

7.1 Introduction

The clinical diagnosis of undescended testes (UDT) in competent hands usually is straightforward [1]. However, the number of children referred to paediatric surgical clinics with 'retractile testes' which could not be located by the primary referring practitioner, or who present later in childhood (or at infertility clinics as adults) with previously unrecognised cryptorchidism, testifies to the difficulties of making a correct diagnosis, particularly if the boy is developing acquired, ascending UDT. This chapter describes the technique of examination and the methods available for the investigation of the common undescended palpable and uncommon impalpable testis.

7.2 Aims of Clinical Examination

The purpose of clinical examination is (1) to identify the presence and location of a testis and (2) to determine the lowest position in the line of normal descent that it can achieve. All testes have a range of movement, and it is the lowest limit of this range, without tension on the spermatic cord, which is relevant. The lowest limit of the testicular position probably corresponds with the caudal limit of the processus vaginalis (PV).

7.3 Technique of Examination

The examination should be conducted in warm surroundings with the infant or child relaxed. He should lie on a comfortable examination couch which is at a height comfortable for the clinician. When his clothing is removed to expose the genitalia, the appearance of the scrotum and any swellings in the inguinal region are noted. The position of the testes is then confirmed by palpation. In infants who are still in

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nappies, the scrotum should be inspected immediately after removing the nappy, as heat under the nappy ensures cremasteric muscle relaxation, which is lost as the ambient temperature falls.

7.3.1 The Appearance of the Scrotum

There is considerable variation in the appearance of the scrotum at different ages and body types (Fig. 7.1). When a testis is obviously in the scrotum at the commencement of examination, its exact location should be noted: whether it is at the bottom of the scrotum, the mid-scrotum, or top (and subsequently whether it retracts out of it).

If two testes are seen lying spontaneously low in the scrotum, cryptorchidism is not present (Fig. 7.2). An empty hemiscrotum is suggestive of UDT, 'retractile' testis, or absent testis. When there is a retractile or ascending testis, the scrotum is usually well developed and similar to the contralateral side. An empty hemiscrotum of reasonable size suggests that the examiner could expect to bring a testis down into it, i.e. a retractile/ascending testis is likely [2] (Fig. 7.3). A flat, small hemiscrotum is less likely to have had a testis residing in it (Fig. 7.4) but is not diagnostic of cryptorchidism.

7.3.2 Location of the Testis

When one or both halves of the scrotum are empty, the position of the testis(es) should be determined. In Fig. 7.4, one testis is fully descended, whereas the other is out of the scrotum. When a testis is not evident in the scrotum, it is most likely lying in the superficial inguinal pouch, lateral and superior to the pubic tubercle (see

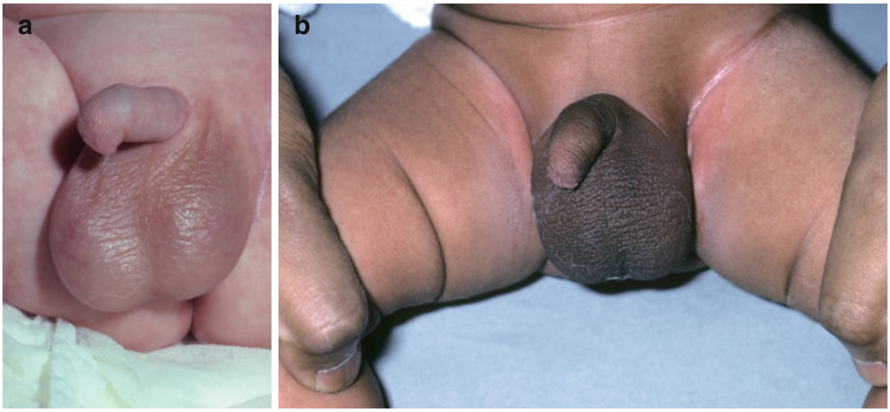


Fig. 7.1 The different appearances of the scrotum at birth; (**a**) the thin, redundant and large scrotum of a neonate; and (**b**) an even more redundant neonatal scrotum containing hydroceles

Fig. 7.2 Normally descended testes readily seen lying in the scrotum of an 8-yearold boy

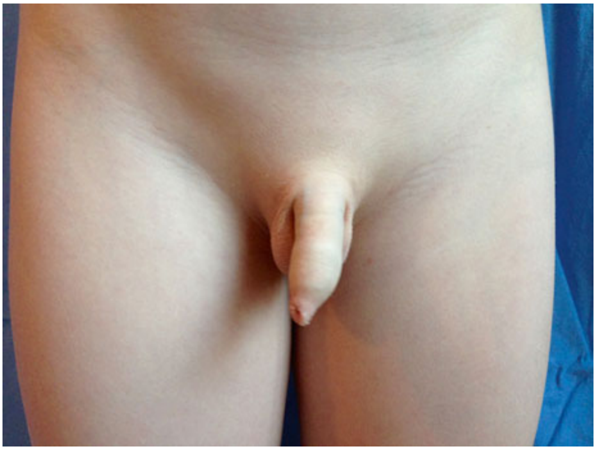
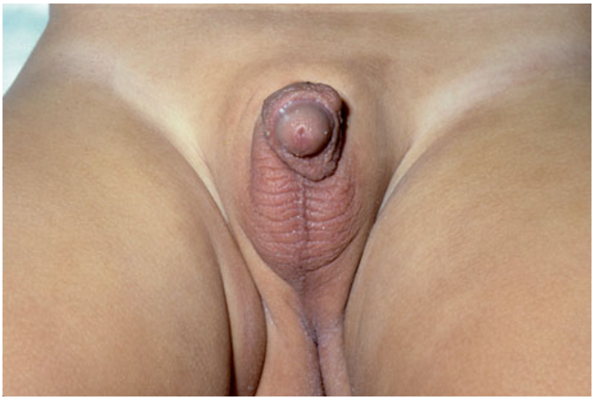


Fig. 7.3 Where there is a unilateral retractile testis, both sides of the scrotum are of the same size, as both testes descended and were in the scrotum in the first year



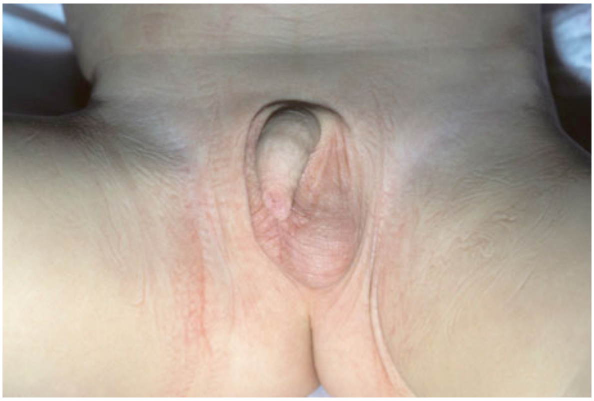


Fig. 7.4 A flat small hemiscrotum suggests the ipsilateral testis does not normally reside in it

Chap. 4). It can best be felt with the flat of the fingers of one hand which milk it downwards and medially along the line of the inguinal canal towards the scrotum (Fig. 7.5).

While the testis is being moved over the pubis, the thumb and index finger of the other hand can grasp it through the scrotal skin to assess the lowest level to which it can be manipulated (Fig. 7.6). In this way, the testis is brought (if possible) into the scrotum and its exact and lowest position noted. If tension on the cord prevents the testis reaching the bottom of the scrotum, the testis is undescended. It is also undescended if it can be pulled to the bottom of the scrotum under tension, but disappears out of the scrotum as soon as it is released (Fig. 7.7). If the testis can be released in the scrotum yet remains there for a short period before the cremasteric reflex returns it to the suprascrotal or inguinal position, it is described as being descended but ‘retractile’. Once a retractile (but descended) testis has been brought into the scrotum in this way, it can be released and observed, still within the scrotum, by drawing back the fingers overlying the pubic tubercle.

A canalicular or ‘emergent’ testis may be impalpable initially and only appear when it is ‘milked’ out of the inguinal canal (where it is concealed from detection

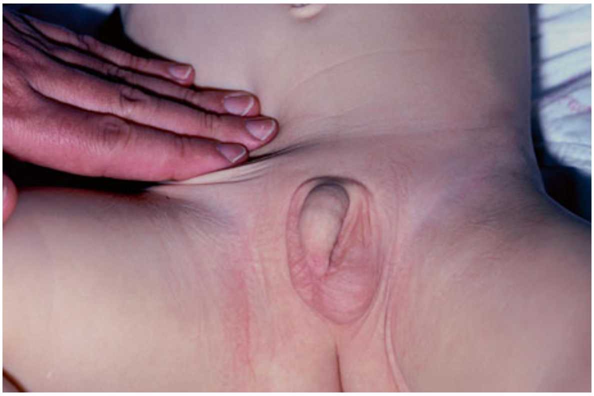


Fig. 7.5 The right UDT that is lying in the superficial inguinal pouch can best be felt with the flat of the fingers, which then ‘milk’ it down towards the scrotum

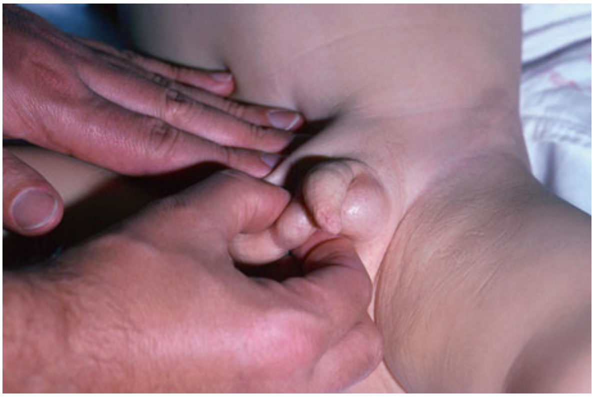


Fig. 7.6 When the testis is coerced over the pubis, the thumb and index finger of the other hand can grasp it through the scrotal skin to assess the lowest level to which it can be manipulated

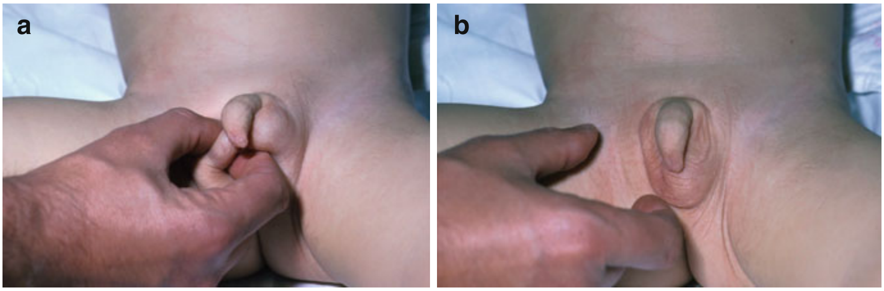
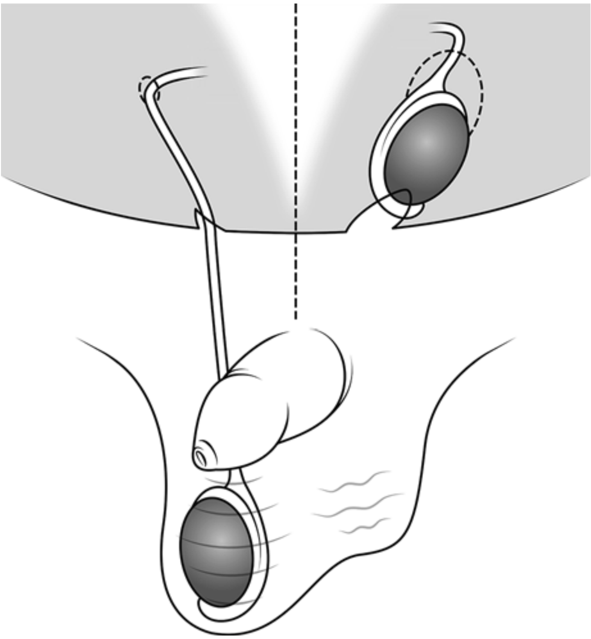


Fig. 7.7 (**a**) The UDT can be held through the skin, but when it is released (**b**) it disappears from the scrotum

Fig. 7.8 A physical characteristic of a canalicular testis is that the external ring is often stretched open, and is palpable as a v-shaped gap in the external oblique aponeurosis



by the overlying external oblique aponeurosis) to emerge at the external ring at which level it becomes palpable (and hence detectable clinically). A canalicular testis is impalpable until it can be milked out of external ring, which is usually palpably open: an important physical sign when no testis is felt on preliminary examination (Fig. 7.8).

7.3.3 Description of the Level of the Testis

There are two main methods by which the positions of testes have been classified. The first was popularised by Scorer [3] who described a testis as being cryptorchid

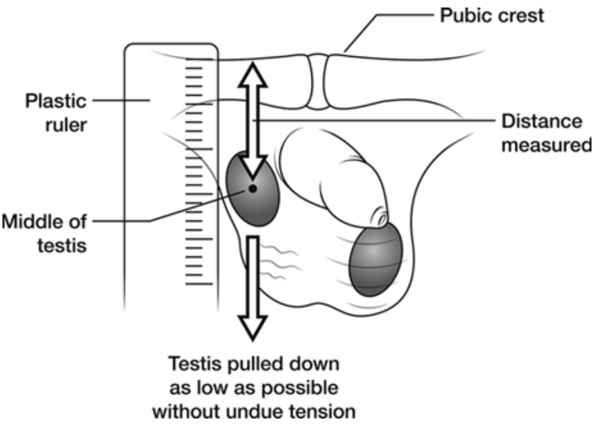


Fig. 7.9 Measurement of the distance of descent from the pubic tubercle, measured with a plastic ruler

if the centre of the testis was less than 4 cm below the pubic tubercle and 2.5 cm at the birth examination for babies weighing under 2500 g. All measurements were rounded down to the nearest 0.5 cm. Measurement is made after the testis is manipulated into its lowest position along the pathway of normal anatomical descent, without undue tension being applied to it (Fig. 7.9). Application of these criteria defines a UDT by measurement [4]. This method of documentation requires considerable precision and is only practicable in a research setting.

The second, and perhaps the more popular, method is to define the UDT by position [5]. The position of each testis was classified as being normal (well down in the scrotum), high scrotal, suprascrotal (palpable, and in line of normal descent including the superficial inguinal pouch, but not in the scrotum—see Chap. 4), nonpalpable, and ‘others’. The latter included ectopic, neonatal orchidopexy before examination, and position obscured by a hernia or hydrocele. This system classifies all testes which are not well down in the scrotum as being undescended. This method has a close correlation with that described by Scorer.

7.3.4 Examination of the Newborn

Scorer in 1956 [3] observed that the lower the birth weight, the higher the incidence of cryptorchidism. This observation is now a common occurrence with the increased survival of infants before 30 weeks’ gestation, i.e. before inguinoscrotal descent is complete. This applies even when premature babies are examined 3 months after their expected delivery date, rather than according to their chronological age, thus correcting for effects of low gestation by allowing extra *time* for the testes to descend spontaneously [5].

The effective gestational age is an important factor in addition to that of birth weight. The Oxford follow-up study [5] in the 1980s showed that testes of cryptorchid babies of less than 37 weeks’ gestation are more likely to descend by the age of 3 months than in babies of longer gestation. The lower the testis is along the path of normal descent at birth, the higher the chance that the testis *will* descend spontaneously by 3 months of age [5]. The John Radcliffe study found that testes at the level of the pubic tubercle (i.e. zero measurement) have half the chance of spontaneous descent of those which are definitely below the pubic tubercle. The latter group is as likely to descend as the high scrotal testis.

The majority of boys born at full term have both testes fully descended in a large thin-walled scrotum. Testes are easily visible and palpable and readily reach the bottom of the scrotum, which is proportionately much larger than later in childhood (see Fig. 7.1a). On measurement, the testes are usually found 4–7 cm below the pubic crest [6].

When a testis is not fully descended at birth, some descent may continue for up to 12 weeks following birth. Where no testis can be felt at birth, it is unlikely that full descent will still occur (except in the extremely premature). Descent ceases altogether after about 3 months of age in most babies. It is possible, therefore, by repeated examination of infants at 3 months of age, to obtain an accurate idea of where the UDT is ultimately going to lie, i.e. the lowest level to which it will descend [6]. There is no evidence that significant descent of the testis occurs in a full-term infant beyond 3–4 months of age. In a study of 3534 boys [5], 210 (5.9 %) were cryptorchid by measurement and 220 (6.2 %) by position at birth. By 3 months of age, the rate of cryptorchidism was identical (1.6 %) in both groups.

7.3.5 Examination of the Premature Infant

Because inguinoscrotal descent of the testis occurs in the seventh month of gestation, infants born at this time will often demonstrate UDT. The position and movement of the testes in these infants is easy to observe because the testis is relatively large at a time when there is little subcutaneous fat and the scrotum is undeveloped and relatively small compared to the full-term baby. The great majority of testes in these infants descend normally, and descent will be complete by term. There is also a higher incidence of inguinal herniae If a testis is still undescended at 3 months post-term, it will remain so. As in full-term infants, the left testis is more commonly affected than the right.

7.3.6 Mobility of the Testis

The great mobility of the testis within, and out of, the scrotum is permitted because (1) the testis has no direct attachment to the scrotum and (2) the testis is on a mesentery (the ‘mesorchium’) inside a patent PV [7]. Non-adherence to the scrotum can be demonstrated by locating a fully descended testis in the scrotum and then displacing it upwards into the groin without any evidence of retraction or inversion of the scrotal skin. If, however, the testis is displaced even further from the scrotum (and distal attachment of the gubernaculum), inversion at the site of gubernacular attachment occurs. In a normally descended testis, this is to the inside of the scrotum, while in a UDT, the attachment will be to the subcutaneous tissues above the neck of the scrotum.

7.3.7 Cryptorchidism Associated with a Symptomatic Hernia

Normally, the patent processus vaginalis (PV) begins to close proximally only after the testis has descended through it to the scrotum, as in the human (as compared to other mammals) obliteration of the PV lumen is thought to be the last step in testicular descent. In the premature infant in particular, the testis is still occupying the PV, holding it open, and with the effect of peaks in intra-abdominal pressure (e.g. crying), herniation of bowel through the internal ring is more likely to occur. This may explain in part the apparent increased frequency of symptomatic herniae in the premature infant.

Occasionally, a strangulated inguinal hernia may occur in an infant who has a UDT (Fig. 7.10). The infant presents with a tender, irreducible lump at the external ring, and the ipsilateral scrotum is empty. Careful examination will reveal two components to the lump, one being the testis and the other the contents of the hernial sac. Gentle manipulation of the hernial component usually achieves its reduction, and at subsequent surgery orchidopexy is performed at the time of herniotomy. Failure to site the testis in the correct position in the scrotum at this time creates major technical problems later, since adhesions and scar tissue in the region of the internal inguinal ring make a later orchidopexy difficult.

A long-standing or tightly strangulated inguinal hernia can interfere with the blood supply to the testis. This may be evident at the time of herniotomy and orchidopexy, e.g. blood-stained fluid around the testis, or on review later, when the testis atrophies and disappears. Injury to the testicular vessels during the operative procedure may also cause testicular atrophy, a reason that this procedure is best performed by a paediatric surgeon, whose expertise and familiarity with the region in infants makes inadvertent injury to the vascular supply of the testis less likely.

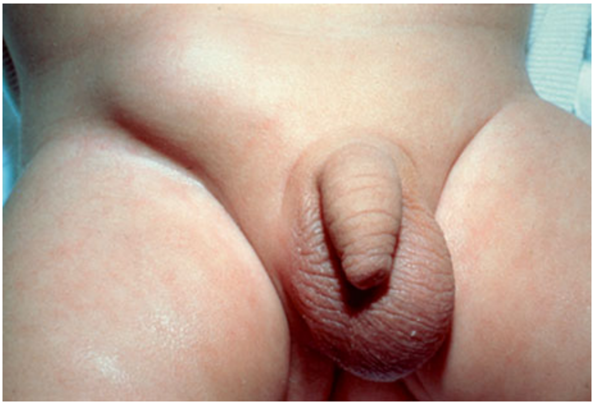


Fig. 7.10 A strangulated inguinal hernia with an ipsilateral UDT and contralateral hydrocele

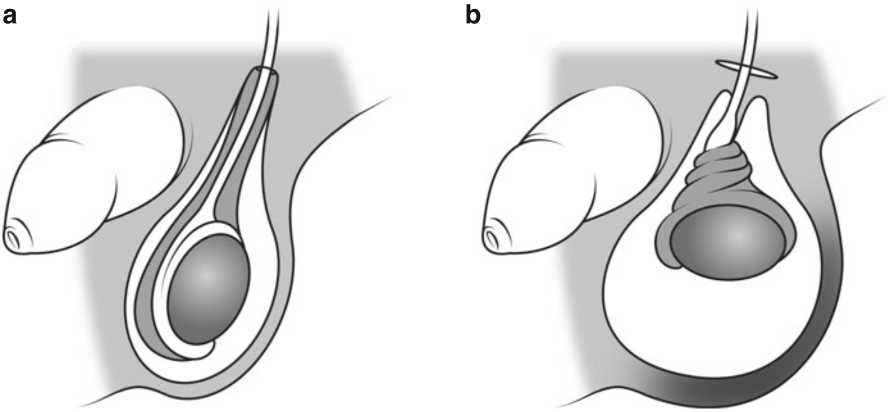


Fig. 7.11 (**a**) A testis undergoing torsion is usually suspended on a long mesorchium, which shortens during the process of twisting, resulting in (**b**) the testis assuming an apparently higher position in the scrotum

7.3.8 Apparent Cryptorchidism with Testicular Torsion

Testicular torsion is most common during adolescence in boys with fully descended testes (only rarely are UDT involved), although testicular torsion is more common in cryptorchid than descended testes. However, when the mesorchium of the testis, which contains the testicular vessels and vas deferens, twists, the testis is lifted up towards the neck of the scrotum, which might give a false impression of the testis being 'high' to start with (Fig. 7.11). It is almost certain that the testis was descended fully prior to the torsion.

7.4 Undescended Versus Retractile Testis

A UDT must be distinguished clinically from a 'retractile' testis, which may be in the grey zone between a normally descended testis and an ascending, acquired UDT. A UDT cannot be manipulated to the bottom of the scrotum and remain there: even if it can be coerced into the upper scrotum, further traction on it causes pain (from stretching of the spermatic cord), and as soon as it is released, it adopts its original position out of the scrotum. On the other hand, a retractile testis may be found initially outside the scrotum but can be brought down into a normal position in the scrotum, a reflection of the normal range of movement the child's testis is allowed. After manipulation into the scrotum, the testis stays there until the cremasteric reflex is stimulated [8, 9].

In the majority of normal boys, the testes are always at the bottom of the scrotum; the cremasteric reflex produces a small upward movement, although the testes do not normally leave the scrotum [2]. There are many boys in whom one testis is stable at the bottom of the scrotum and the other one retracts. It is now recognised

Table 7.1 Characteristics of the retractile testis (which currently does not need orchidopexy)

1.	Can be brought fully to the bottom of the scrotum
2.	Remains in the scrotum for a period before retracting (retraction is immediate if the cord is tight and the testis undescended)
3.	The testis resides spontaneously in the scrotum at times
4.	The testis is a normal size

that many ‘retractile’ testes become higher as age increases and are developing into an ascending testis with acquired cryptorchidism [2, 9–14]. Thus, it is important to consider the age of the child in relation to the position of the testis in the scrotum.

The main characteristics of a retractile testis are summarised in Table 7.1. Two features which may be useful in distinguishing retractile testes (which may need observation, but not surgery) from UDT (which need surgery) are testicular size and pain and tightness in the spermatic cord on traction.

7.4.1 Testicular Size

If the testis in question is smaller than an opposite normally descended testis, retarded development (i.e. dysplasia) related to incomplete descent is likely, which is an indication for surgery.

7.4.2 Pain and Tightness in the Spermatic Cord

A normal testis can be held between the finger and thumb and traction exerted on the cord without causing pain. When the cord is abnormally tight, this manoeuvre causes pain at the lateral end of the inguinal canal, the site of the lateral suspensory fibres, and the connection of the PV to the main peritoneum found at orchidopexy [2]. This suggests the spermatic cord may contain a fibrous remnant of the PV and the possibility of developing into an ascending testis is high.

The difficulty distinguishing a ‘retractile’ testis from a UDT has prompted some clinicians to use human chorionic gonadotrophin (hCG). The rationale for treatment is that in retractile and ascending testis, hCG would be expected to induce testicular descent because testosterone has been produced. Failure of hCG to achieve descent (and inhibit retractility) would suggest the testis has developed into an ascending testis with acquired UDT.

7.5 Clinical Features of Ectopic Testes

7.5.1 Definition

When the gubernaculum (with its contained testis) has migrated away from the normal pathway of descent or the testis, it is said to be ectopic. It may occupy one of a wide variety of positions in the inguino-perineal region (Table 7.2). An ectopic testis may have a normal length of spermatic cord and simply require relocation in

Table 7.2 Ectopia of the testis

Perineal testis
Pubopenile testis
Femoral testis
Crossed testicular ectopia
Exstrophy of the testis
Ectopia of the scrotum
Within a Spigelian hernia

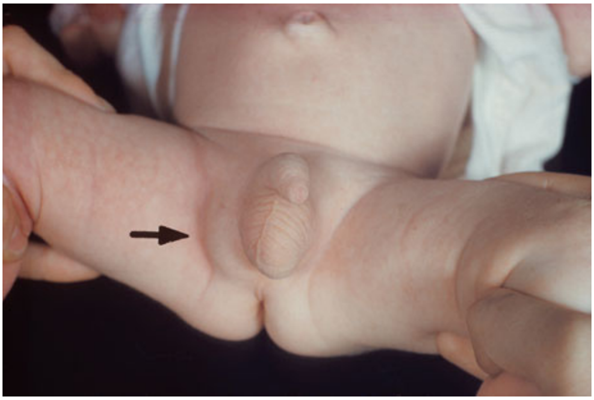


Fig. 7.12 A perineal ectopic testis (shown by *arrow*) where the testis has migrated past the scrotum to reach the perineal body

the scrotum. By the definition provided above, a testis in the superficial inguinal pouch is not considered ectopic (see Chap. 4).

7.5.2 Perineal Testis

The infant presents with an empty hemiscrotum and an adjacent perineal swelling (Fig. 7.12). If unrecognised at birth, it may present later in life with perineal pain following sitting in certain positions. The swelling is behind the scrotum but anterior to the anus and to one side of the median raphe [6]. The long axis of the testis is directed anteroposteriorly. There is usually a normally descended testis on the other side: bilateral cases are rare but occasionally there may be a UDT on the other side. The perineal testis is well developed and normal in size initially, and the epididymis has a normal relationship to the testis, but it suffers the same temperature-dependent-degeneration as in other UDT.

The spermatic cord of the perineal testis is of ample length, which allows for easy mobilisation into the scrotum during orchidopexy.

7.5.3 Pubopenile Testis

In this rare condition, the testis is found to lie subcutaneously on the dorsal aspect of the penis near its base, close to the pubic bone [6].

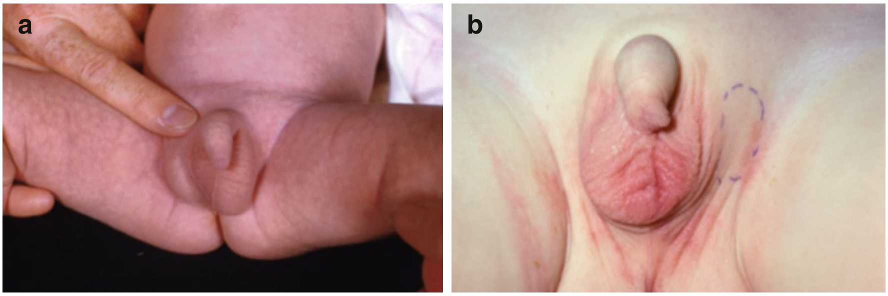


Fig. 7.13 An inguino-perineal testis lying lateral to the empty hemiscrotum (**a**) A right-sided inguino-perineal testis showing examining hand immobilising spermatic cord to enable testis to be seen. (**b**) A left inguino-perineal testis with skin marking highlighting that it is easy to miss on inspection

7.5.4 Femoral Testis

A femoral location is a rare place for an ectopic testis. Usually it has descended through the inguinal canal but then migrated infero-laterally into the subcutaneous tissue of the thigh. However, descent of the testis through the femoral canal has been reported [15]. The lower end of the gubernaculum appeared to occupy the femoral ring, but occasionally the testis still managed to reach the scrotum [16].

7.5.5 Inguino-Perineal Testis

The inguino-perineal ectopic testis may be found initially in the superficial inguinal space but cannot be manipulated into the scrotum. Instead, it passes lateral to the scrotum. In other boys it may be identified residing spontaneously lateral to the scrotum in the medial aspect of the upper thigh or even beyond the scrotum (Fig. 7.13).

7.5.6 Crossed Testicular Ectopia

In this rare condition, one testis descends (usually incompletely) down the contralateral PV [17]. It has been discussed more fully in Chap. 4.

7.5.7 Testicular Exstrophy

In this extremely rare condition, the testis is exposed through a defect in the skin of the neck of the scrotum [18] (Fig. 7.14). A potential explanation for this anomaly proposed by Stephens [19] is that there is local compression of the scrotum by the heel of the fetus, leading to skin necrosis, with secondary prolapse of the testis through the defect.

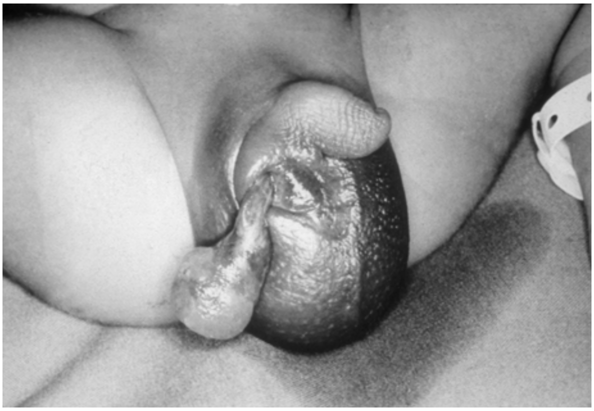


Fig. 7.14 Exstrophy of the testis, which is protruding through a defect in the hemiscrotum. This is likely to be caused by a pressure sore on the scrotum by the heel of the fetus' foot (Photo kindly provided by Prof. Chris Heyns [18])

In very rare circumstances, the UDT may be located in an ipsilateral Spigelian hernia [20], where it is likely that the initial location of the gubernaculum was misplaced, possibly by an anomaly of embryonic segmentation. On examination the testis may be indirectly palpable as part of the hernial contents of the lump about halfway between the inguinal ligament and umbilicus, at the lateral edge of the *rectus abdominis* muscle [21, 22].

7.5.8 Ectopia of the Scrotum

In these rare infants, the testis descends normally into the scrotum but the scrotum itself is ectopic [23, 24]. Abnormalities of the genito-urinary and skeletal systems are common associations of this bizarre defect which is likely to be caused by fetal deformation [19] (Fig. 7.15).

7.6 Impalpable Testis

7.6.1 Purpose of Investigation

Most UDT have migrated at least as far as the external inguinal ring with little abnormality of the transabdominal phase. If a testis is impalpable when examined by an experienced paediatric clinician (usually a paediatric surgeon), it means that it is either:

(a) Absent
(b) Intracanalicular or intra-abdominal

If a testis is present, it should be identified because of the risks of malignancy and infertility.

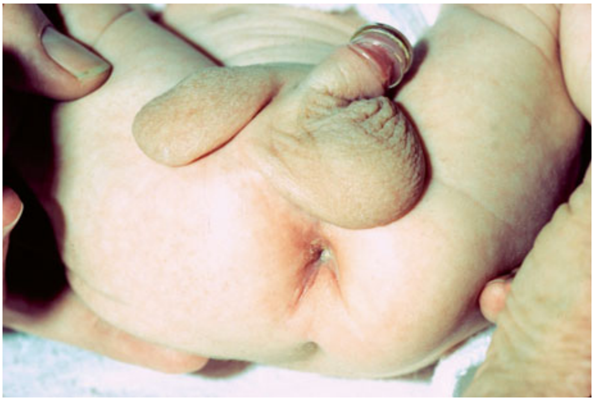


Fig. 7.15 A disrupted right hemiscrotum caused by extrinsic pressure of the fetus' right heel in a baby with an anorectal malformation with a cutaneous fistula

Table 7.3 Investigation of the impalpable testis

1.	Imaging techniques	Ultrasound (magnetic resonance imaging)
2.	Laparoscopy	
3.	Hormonal tests	AMH and inhibin-B levels (shows presence of Sertoli cells)
		hCG stimulation (shows presence of functional Leydig cells by androgen production)

7.6.2 Clinical Examination

Many apparently 'impalpable' testes, when the child is examined by a primary medical practitioner, can be palpated by a paediatric surgeon. This is most likely to occur in an older child who has markedly 'retractile' testes that are developing into ascending, acquired UDT. Alternatively the boy may be obese, where the testis was not detected in the groin because of its mobility and/or the thick overlying layer of subcutaneous fat. Every effort should be made to coerce a potentially intracanalicular testis through the external ring, as described earlier in this chapter. Failure to achieve this will necessitate performance of one or more of the investigations summarised in Table 7.3.

Infants and small children with bilateral impalpable testes should have an ultrasound scan and either an hCG stimulation test or AMH and inhibin-B combined with FSH blood levels measured [25] to confirm that functional testicular tissue is present.

7.6.3 Ultrasonography

An ultrasound scan is a non-invasive test which has been used to identify impalpable testes [26]. Ultrasonography is reasonably successful in the search for intracanalicular testes but is of much less value for the intra-abdominal testis [27, 28]. Ultrasonography is a useful tool in identifying the intracanalicular testis and is also effective in documenting the testicular size and has been used in recent studies to demonstrate improved testicular growth after orchidopexy at 9 months compared with 3 years [28].

7.6.4 Magnetic Resonance Imaging (MRI)

MRI is a non-invasive, non-ionising method of locating UDT, capable of obtaining multiplanar images. It has been shown to identify clearly bilateral intra-abdominal testes in an adult [29]. The potential additional benefit of localisation of an impalpable testis with MRI is that it may provide information on tissue characteristics [27], but sedation or anaesthesia may be needed in children under 5 years of age.

Extra-abdominal testes can be demonstrated in both the coronal and transaxial planes with reasonable reliability [30].

7.6.5 Laparoscopy

Laparoscopy is the ‘gold standard’ for locating intra-abdominal testes (Fig. 7.16). It is based on the assumption that since the vas deferens and epididymis are rarely separated completely from the testis, visualisation of the vas will lead to the testis if it is present. In addition the testis can always be located by following the testicular vessels to their destination.

Diagnostic laparoscopy for impalpable testes allows the surgeon to plan the surgical approach [31] and perform laparoscopic one- or two-stage orchidopexy and avoid unnecessary laparotomy.

A second, less common indication is in the older child who has undergone previous (but deemed inadequate) open inguinal exploration, where either no testis was identified or only a vas with no testicular vessels was seen [32, 33].

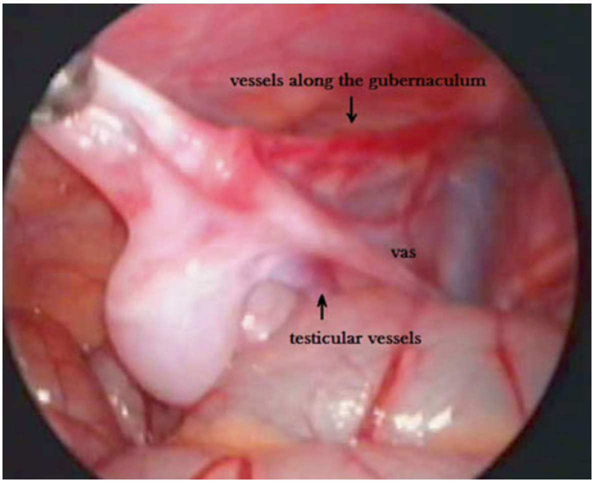


Fig. 7.16 An intra-abdominal testis on its mesorchium, showing the testicular vessels and collaterals from the cremasteric artery in the gubernaculum

The primary objective is to see the internal ring [34]. When the testis has descended beyond the internal ring, the retroperitoneal leash of testicular vessels is joined by the whitish vas deferens as a 'V' at this ring, and it has a characteristic appearance. When the testis is impalpable, the most common finding is that of a testis which is readily seen lying within a centimetre or two of the internal ring. If the intra-abdominal testis is not immediately apparent, it can be traced by following the testicular vessels, and if the vessels appear much smaller than normal and their course takes them into the inguinal canal, it is likely that there is no testis present. If the vessels and blind-ending vas deferens lie contiguously—the so-called vanishing testis—it is likely that at some time in embryological development, a testis was present [35].

Very occasionally, there may be no evidence of a vas or vessels within the accessible peritoneal cavity. This suggests true congenital absence of the testis, but extensive dissection up to the lower pole of the kidney may be required to confirm testicular agenesis [34].

Conclusion

In many centres, there is a trend towards imaging by ultrasonography of patients with both unilateral and bilateral impalpable testes. Unfortunately, for the testis for which accurate localisation would be useful, i.e. the intra-abdominal testis, the technique is unreliable. The preferable first step, therefore, in the management of a patient in whom a testis is not palpable should be referral to a paediatric surgeon who is skilled in examining the inguinal region an infant and boy [36]. Many previously 'impalpable' testes then become 'palpable', and no further preoperative investigation is required.

Laparoscopy is now the 'gold standard' for impalpable undescended testes (along with AMH/inhibin-B measurement to confirm presence of testicular tissue). It has a high degree of reliability and accuracy and can be performed under the same anaesthetic as the subsequent orchidopexy (when indicated). The surgeon should be aware of the rare situation of complete separation of the testis and vas deferens and the absence of the testis.

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Operative Treatment

8

8.1 Planning Surgery

Surgery is currently the only effective and reliable way of bringing the undescended testis (UDT) into the scrotum; this chapter describes in detail the surgical procedures which can be employed [1]. Orchidopexy is usually a straightforward procedure, but occasionally the short length of spermatic cord available or the flimsy inverting hernial sac (particularly with the intracanalicular testis) may create operative difficulty. On other occasions, the presence of Müllerian structures, testicular–epididymal fusion abnormalities, the 'vanishing testis', polyorchidism, absent vas, splenogonadal fusion, or ectopic (adrenal or renal) tissue may cause confusion. The recognition and management of these unusual and difficult situations is discussed.

Meticulous operative technique with careful separation of the processus vaginalis (PV) or hernial sac and exact dissection of the cord to increase its length contribute to the good results now expected after orchidopexy. Orchidopexy is best performed by trained paediatric surgeons who are familiar with handling infantile tissue and who feel comfortable operating with magnification. The 'occasional orchidopexy' is not an operation which adult general surgeons or urologists should be encouraged to perform, unless there are no paediatric surgical facilities available.

8.1.1 Age at Orchidopexy

When paediatric surgery first became a specialty, orchidopexies were performed in the prepubertal child. Since then, there has been a stepwise fall in the age at which orchidopexy has been advocated (Fig. 8.1), mainly as a result of the evidence of testicular damage which occurs in the untreated UDT after infancy [14].

Recently, it has been appreciated that the neonatal germ cell (known as a gonocyte) moves from the centre of the testicular cords at about 3–6 months of age to reach the

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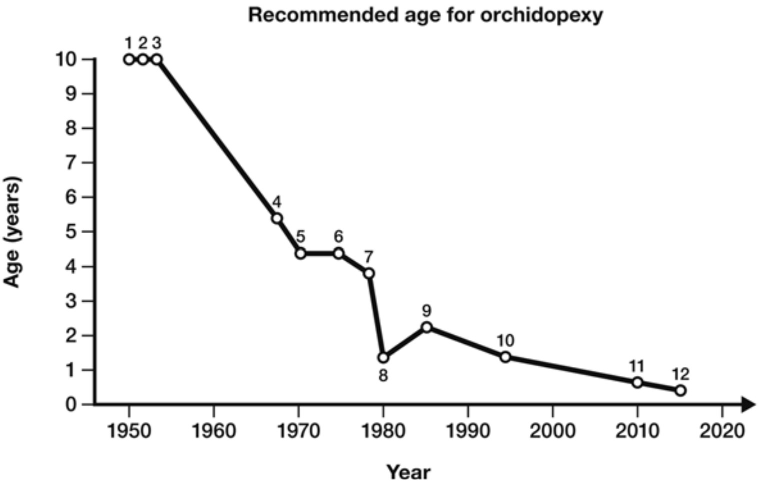

Fig. 8.1 The age at which orchidopexy has been advocated since the 1950s. (*1*) [2]; (*2*) [3]; (*3*) [4]; (*4*) [5]); (*5*) [6]; (*6*) [7]); (*7*) [8]; (*8*) [9]; (*9*) [10]; (*10*) [11]; (*11*) [12]; (*12*) [13]

basement membrane, where it transforms into a type A spermatogonium, which is now thought to be the spermatogenic stem cell [15]. This has led to the recommendation that orchidopexy should be done somewhere between 3 months (after late spontaneous postnatal descent is complete) and 9–12 months (after which time significant germ cell loss takes place in UDT). Taking the anaesthetic risk for elective surgery into account, many paediatric surgical centres currently recommend orchidopexy at 6 months of age [16], although anytime up to 12 months is probably acceptable.

If a clinically evident hernia appears in an infant who has an ipsilateral UDT, an orchidopexy should be performed at the same time as the herniotomy, irrespective of the age of the infant. Failure to do so would make subsequent orchidopexy extremely difficult, due to fibrous adhesions in the region of the internal ring.

Good paediatric surgical technique, facilitated by the use of loupe (magnifying) glasses, means that orchidopexy can be performed with great accuracy and safety in infants.

Repeated careful examination of older children with markedly retractile testes may identify ‘ascent’ of the testis—this testis is often brought down at the time it is first recognised to have become ‘cryptorchid’ (i.e. it is no longer able to reside spontaneously in the scrotum).

8.1.2 The Day Surgical Procedure

Orchidopexy is performed as a day surgical procedure. The infant is admitted to the day surgical ward an hour or so before surgery, where he is re-examined and seen by the anaesthetist. In most centres, the parents remain with the baby until he is asleep and are again present once he leaves the operating or procedure room.

The infant is allowed to leave the day surgical facility once he is fully awake from the anaesthetic and has been fed. It is not necessary to wait until he has passed urine. Where local or regional anaesthetic agents have been used, it is preferable to have the infant home before their effect has worn off. The parents—and the child, if old enough—should be informed of the likely intensity and duration of postoperative discomfort. The use of subcuticular absorbable sutures means that there is no trauma of suture removal. Waterproof dressings (or tissue glue) allow normal bathing and water activities in the early postoperative period and avoid the need for wound care. The ultimate cosmetic result for an incision made in the lap crease is excellent.

8.1.3 Anaesthesia

The type of anaesthetic offered to infants and children undergoing orchidopexy reflects the day surgical nature of the procedure. The aim of the anaesthesia is not only to have the child totally unaware of the operation taking place but also to have him wake up quickly and fully, to be in little discomfort, so that he may go home promptly and with minimal psychological and physical trauma.

8.1.3.1 Premedication

In the majority of infants, no premedication is required. The provision of enlightened ‘child-friendly’ day surgical facilities and the acceptance of parents being with the child right up to and including induction of anaesthesia remove most of the anxiety and agitation which previously necessitated the use of premedication agents.

Instead of a ‘pre-med’, it is better to apply local anaesthetic cream to the back of the hand so that when the intravenous inducing agent is to be given, the infant will experience no pain. Indeed, if distracted to look the other way, he will usually be unaware that intravenous access has been obtained.

8.1.3.2 The Use of Regional or Local Anaesthesia

An ilio-inguinal nerve or sacral epidural (in bilateral cases) block or local anaesthetic injected into the wound edges provides satisfactory pain relief for the first few hours postoperatively.

8.2 The Standard Orchidopexy

The standard orchidopexy for a palpable testis involves an inguinal incision, full exposure of the inguinal canal, separation of the PV or hernial sac, mobilisation of the cord structures, and trans-scrotal fixation of the testis in a subdartos pouch. Trans-scrotal orchidopexy [17] also has now gained widespread acceptance.

8.2.1 Approach to Inguinal Canal

The inguinal canal is approached through a transverse lap crease incision (Fig. 8.2) and the wound deepened to Scarpa's fascia. Diathermy dissection achieves this with minimal blood loss. In an infant Scarpa's fascia is a relatively well-formed and substantial pale membrane, which can be distinguished from the external oblique aponeurosis by its absence of oblique fibres. Once Scarpa's fascia has been incised, the wound can be developed and exposed using square-ended retractors: this dissection is continued as far as the external oblique aponeurosis itself. A sweeping motion parallel to the line of the external oblique with scissors separates the fascia and subcutaneous layers from the aponeurosis as far as the inguinal ligament inferiorly.

When this sweeping movement is continued medially, the bifurcation of the fibres of external oblique aponeurosis at the external inguinal ring and the bulge of the spermatic cord become apparent. The inguinal canal can be exposed by either incising the external oblique aponeurosis laterally in line with the external ring or cutting along the fibres towards the ring (Fig. 8.3) or by cutting laterally along the fibres from the external ring.

8.2.2 Identification of Testis

The approximate position of the testis will usually be known prior to surgery. In the most common situation where the testis is just outside the external inguinal ring and overlying the pubic bone, it will be observed first during the approach to the inguinal canal. Within its PV that extends from the external

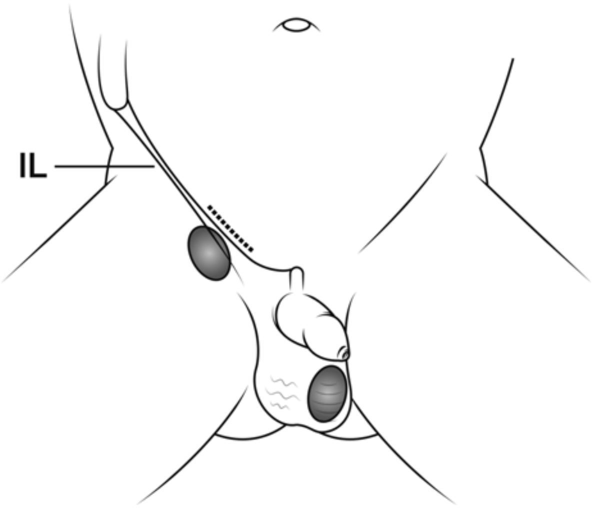

Fig. 8.2 The incision for orchidopexy is made through the transverse lap skin crease. *IL* inguinal ligament

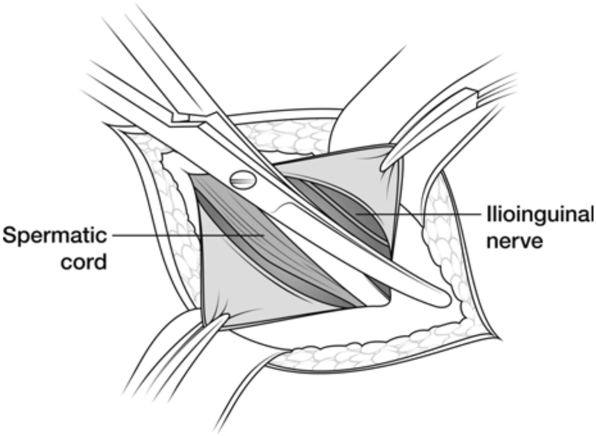

Fig. 8.3 The anterior surface of the external oblique aponeurosis is exposed inferiorly as far as the inguinal ligament by using a sweeping movement with closed scissors. Exposure of the inguinal canal is achieved by incising the fibres of the external oblique aponeurosis to open the external inguinal ring. Alternatively the external ring can be opened by cutting laterally with the scissors after identifying the ring itself

ring, it is often situated immediately superficial to the external oblique aponeurosis. Care should be taken to avoid its damage during opening the inguinal canal.

Where its position is not immediately obvious, the testis can be traced by following the spermatic cord as it continues through the external inguinal ring. Where the testis has been impalpable clinically, repeat examination should be done under anaesthetic, and where no testis is found and the external ring is closed, the surgeon will usually proceed with diagnostic laparoscopy.

8.2.3 Separation of Gubernaculum

A gubernaculum can be found at operation in all patients with UDT [18] and is attached to a site other than the lower scrotum in most.

In UDT the gubernaculum appears to have an abnormal attachment, usually lateral to or above the neck of the scrotum. This can be demonstrated when the testis is lifted out of the wound to place tension on the gubernaculum which then causes the skin adjacent to its attachment to become dimpled.

The testis should be separated from the gubernaculum by teasing the gubernaculum off the tunica vaginalis with broad blunt forceps. If performed at the right level close to the tunical attachment, this procedure is bloodless. This allows the testis to be lifted out of the wound and enables the cremaster muscle to be stripped off the spermatic cord (Fig. 8.4). Sometimes it contains small vessels which require diathermy.

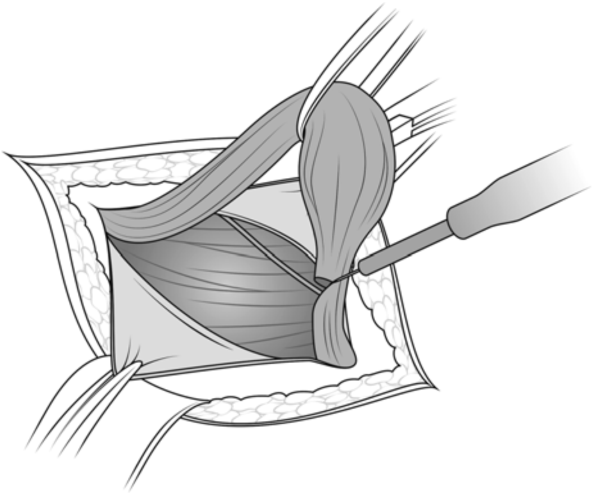

Fig. 8.4 The testis and cord are pulled out of the wound with traction, allowing the cremaster muscle fibres to be stripped off the cord, allowing the gubernacular attachment to be divided

8.2.4 The Hernia Sac

In the great majority of infants with cryptorchidism, there is a widely patent PV [19]. The width of the PV is often of such size that it is interpreted as a hernial sac [18] even though in the vast majority there will not have been a symptomatic hernia. In a study of 68 testes, Jackson et al. [18] found a clearly identifiable 'hernial sac' in 35 (51.5 %) although at what point a patent PV becomes a hernial sac is purely subjective. Scorer documented a 'hernia' in 55 % [20] and Heath et al. [21] in 21.2 %. It should be acknowledged that the incidence of a hernial sac in otherwise normal infants is unknown. By contrast, complete absence of an identifiable PV is extremely unusual. Nevertheless, the significance of a hernia in cryptorchidism is argued [22]. Separation of the hernial sac (patent PV) from the vas deferens and testicular vessels significantly increases the effective length of the cord during orchidopexy.

The method of separation of the sac is the same as that employed during routine herniotomy: the sac is stretched over the index finger while the round-ended non-toothed dissecting forceps gently sweep off the other cord structures, or the sac can be held in forceps while the vessels and vas are isolated en masse off the sac. In this way the sac is completely separated from the cord (Fig. 8.5).

At no stage should either the vas deferens or vessels be held by the forceps; otherwise, they may be damaged. The technique of separation is achieved most efficiently if the sac remains intact. Inadvertent opening of the sac should be recognised early to prevent extension of the tear through the internal ring into the peritoneum, where its closure becomes technically more difficult.

The vas deferens has a tendency to remain adherent to the sac; so it must be ensured that it is seen with the vessels before the sac is divided.

Once the structures of the spermatic cord have been separated from the sac, the sac is divided (Fig. 8.6). The sac is then dissected proximally well into the internal

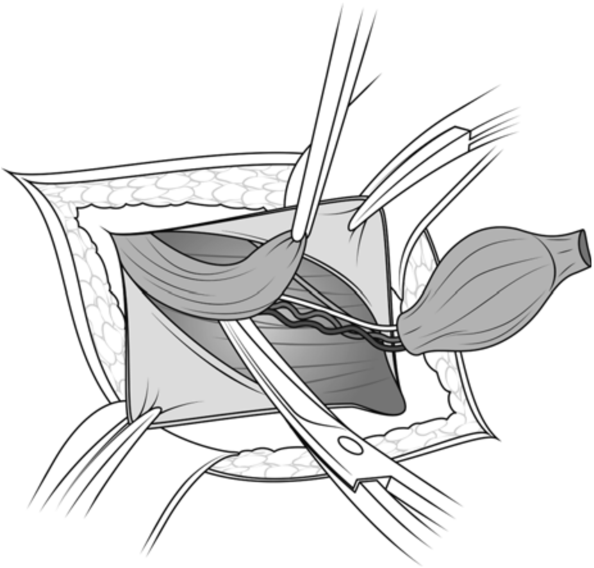

Fig. 8.5 The widely patent processus vaginalis (PV), which forms the hernial sac, is separated from the remaining cord structures in the same as in an open herniotomy

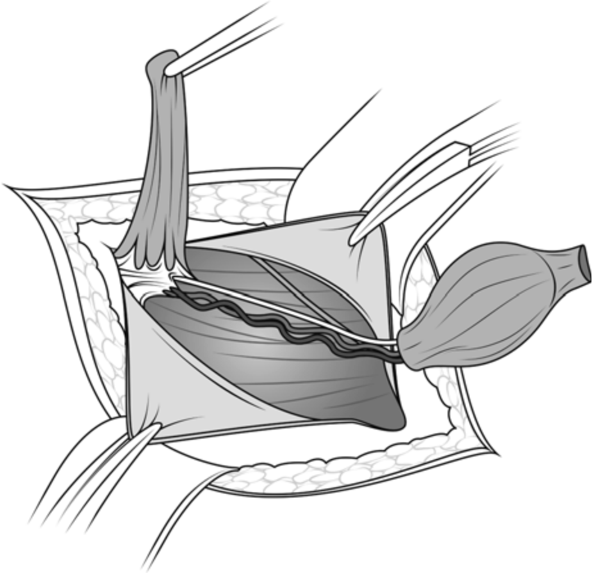

Fig. 8.6 Once completely separated from the vas deferens and testicular vessels, the sac is divided with scissors. Dissection of the sac is then continued to the internal inguinal ring. The hernial sac is transfixed at the internal ring only after it has been fully separated from the remaining cord structures

ring. As the PV merges with the main peritoneum, its appearance changes from transparent to white and its base widens into a triangular structure. At this level the vas deferens can be observed to be deviating medially towards the base of the bladder, while the testicular vessels continue straight into the retroperitoneum in a more lateral position. Extraperitoneal fat is found once dissection reaches above the internal inguinal ring. The hernial sac is transfixed at the internal ring, although recent reports suggest that ligation may not be essential [23].

8.2.5 Freeing the Vessels and Vas

As the testicular artery tracks downwards in the posterior abdominal wall from its origin on the aorta, it crosses the pelvic inlet and follows a gentle curve around the posterolateral concavity of the pelvic cavity to reach the internal inguinal ring, just lateral to the inferior epigastric artery. In doing so, it has thin bands of loose and relatively avascular connective tissue which attach it to the wall of the pelvis; these bands can be demonstrated at surgery when traction is placed on the vessels after separation of the PV. Their division, by straightening the path taken by the vessels, effectively lengthens the spermatic cord and allows the testis to reach the scrotum (Fig. 8.7). They can be divided easily by blunt dissection with non-toothed forceps (by 'teasing' them off the cord) or by sharp dissection with scissors, taking extreme care to avoid damage to the testicular vessels themselves.

Once the manoeuvre is completed, the cord should be fully mobilised with the vas seen curving around the inferior epigastric vessels as it runs towards the base of the bladder and the testicular artery and its accompanying veins free from the lateral pelvic wall and running straight upwards into the retroperitoneum.

As a rule, the vas deferens has sufficient length to reach the scrotum easily [24]. However, if the testicular pedicle is too short, then the Prentiss manoeuvre should be undertaken [25]. The posterior wall of the inguinal canal medial to the inferior epigastric vessels is opened, and the testis is pulled through the space, thereby shortening the path of the testicular vessels and effectively increasing the length of the vas deferens. In some circumstances, the inferior epigastric vessels can be

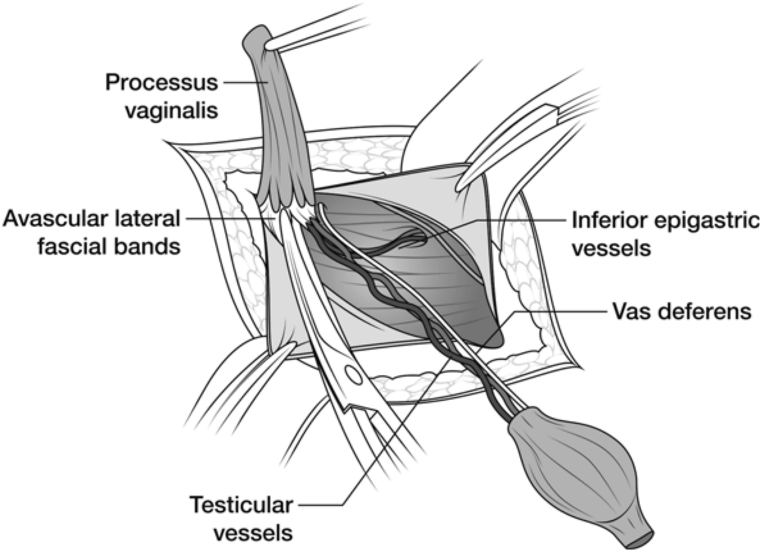

Fig. 8.7 Division of lateral avascular attachments of the cord proximal to the internal ring

transfixed, ligated, and divided to straighten the path of the testicular vessels, which are increased in length about 1 cm in most infants (Fig. 8.8).

8.2.6 Placement of the Testis in Scrotum

After the testis and cord has been adequately mobilised, the testis is placed in the scrotum. This is achieved by first creating a space in the scrotum in which the testis and epididymis can be situated. A midline or transverse scrotal incision is made to gain access to the subdartos space in which the plane is developed by divulsion using scissors or forceps (Fig. 8.9). Some authors [24, 26] describe a pouch in the scrotum between the skin and dartos. Given the attachment of the dartos muscle to the scrotal skin and the absence of muscle deep to this plane in which creation of a pouch is possible, it is likely that they are describing what could more correctly be called a subdartos pouch (Fig. 8.10). Bleeding points are controlled by diathermy. The index finger or a mosquito forceps is then introduced from above along the path intended for the testis, to guide another forceps from below, which is used to grasp the distal tunical coverings of the testis, which are then drawn gently down the track through the 'buttonhole' in the subdartos pouch, into the scrotum (Fig. 8.11). The forceps do not hold the testis itself, thus avoiding direct trauma to the gonad.

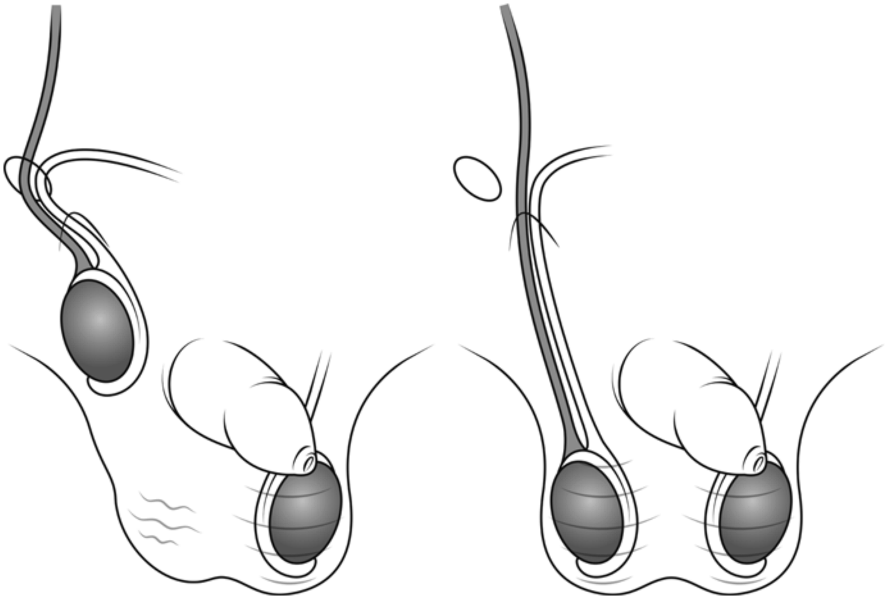

Fig. 8.8 Transposition of the cord structures medial to the inferior epigastric vessels (known as the Prentiss manoeuvre) allows the spermatic cord to take a more direct path to the external inguinal ring. The Prentiss manoeuvre increases the relative length of the spermatic cord by at least 1 cm, even in infants

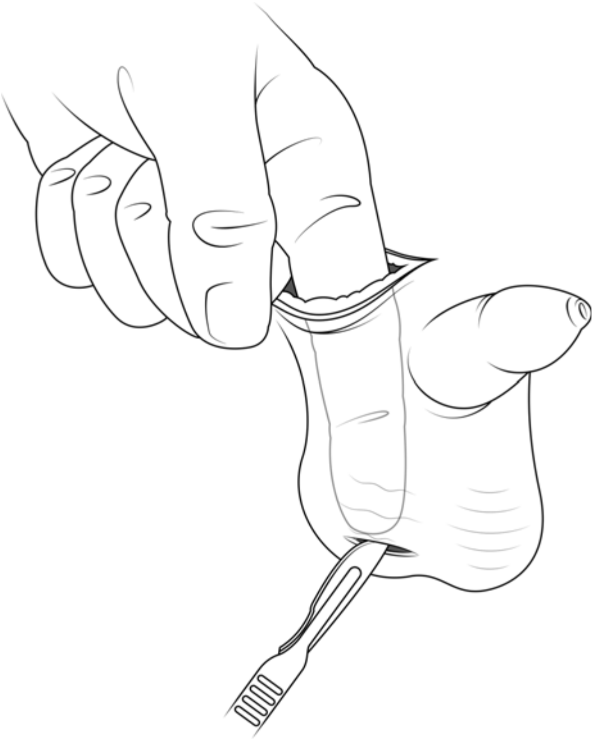

Fig. 8.9 Scrotal incision. Transverse or midline scrotal incision is equally effective

8.2.7 Fixation of the Testis

When the testis is placed into the scrotum, it has to be pulled through the loose fascial layers at the neck of the scrotum. If there is no tension on the cord, this alone will prevent subsequent upwards retraction of the testis. Alternatively, the testis can be anchored to the midline tissue of the scrotum by a 3/0 suture through the tunica albuginea (Fig. 8.12), or the fascial tissues of the neck of the scrotum can be closed to prevent retraction of the testis, taking care to avoid constriction of the testicular vessels. A theoretical advantage of direct anchorage of the testis is in reducing the likelihood (albeit rare) of subsequent torsion [27]. Another advantage of direct fixation after opening the PV is prophylactic excision of any testicular appendages which might cause trouble later in childhood. The scrotum is closed with 4/0 subcuticular or external absorbable sutures.

8.2.8 Dressings and Aftercare

The use of absorbable sutures means that no sutures require removal postoperatively (which is in the child's interests) and ensures a good cosmetic result.

The inguinal wounds are best covered with a sterile dressing or tissue glue/spray which provides a waterproof protection for the wound. The dressing is removed at the postoperative review (if it has not already fallen off). The difficulty in applying

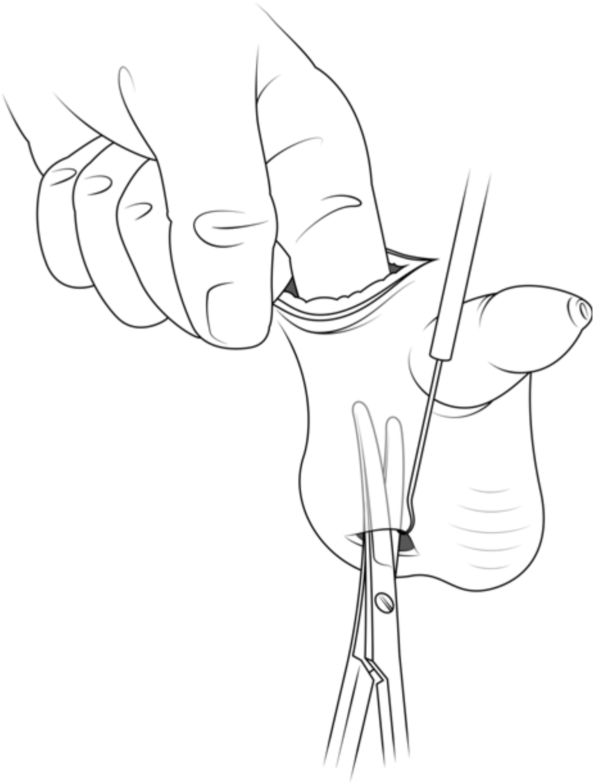

Fig. 8.10 Creation of subdartos pouch

such a dressing on the scrotum and the discomfort caused by its removal (particularly in the older boy) means that the scrotal wound is best covered with a plastic skin spray or tissue glue with no other dressing employed.

Local anaesthetic infiltration of both the inguinal and scrotal wounds and regional nerve blocks ensures good analgesia in the first 4–6 h postoperatively, the period of greatest discomfort otherwise. When the local anaesthesia wears off, paracetamol administered orally is usually adequate to control pain.

The use of local anaesthesia and a light general anaesthetic allows the infant to be discharged from the day surgical centre an hour or two after the operation, ideally so that he will be home and settled before the local anaesthesia has worn off. This makes transfer and transport less of an ordeal for the child (and his parents).

8.3 Unusual Findings During Orchidopexy

8.3.1 Testicular–Epididymal Fusion Abnormalities

In many UDT, particularly 'high' ones in the canal or the abdomen, the epididymis is not normally adherent to the testis [19]. Some variants of testicular–epididymal separation will cause sterility, although as long as the rete testis is intact (Fig. 5.8),

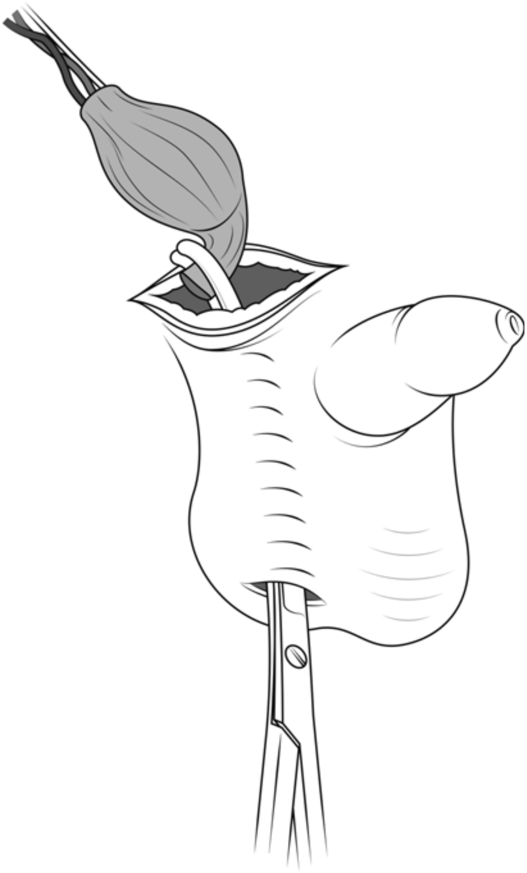

Fig. 8.11 The cord (and testis) is brought into the scrotum

fertility should be normal. Concern over the implications of this anomaly has provoked some authors to recommend very careful documentation of all anatomical variants of testicular–epididymal fusion [28].

8.3.2 Ectopic Tissue

Splenogonadal fusion (Fig. 5.9) is another well-recognised entity which is probably under-reported [29]. It is occasionally seen at the time of left orchidopexy [30]. The splenic tissue should be separated from the left testis and an orchidopexy performed in the usual manner.

Ectopic renal tissue has also been described in association with a UDT [31] but must be extremely rare. A much more common finding, but one which has no significance, is ectopic adrenal cortical tissue in the spermatic cord. It appears as a 1–3 mm hard spherical and bright yellow nodule within the cord—it can be ignored.

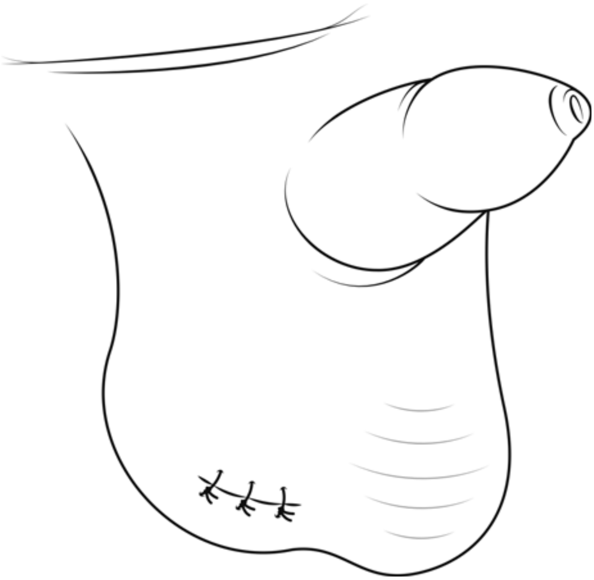

Fig. 8.12 The tunica albuginea of the testis (after opening the tunica vaginalis) can be sutured to the scrotal fascia to prevent postoperative displacement of the testis. Alternatively, some surgeons suture the tunnel through which the testis has been brought down. A simple suture to narrow the tunnel at the neck of the scrotum is sufficient to prevent accidental displacement upwards of the testis. After the testis is placed into its new subdartos pouch, the scrotum is closed

8.3.3 Absent Vas Deferens

Complete absence of the vas deferens is an occasional finding during orchidopexy. This will be seen in infants with cystic fibrosis (CF) and in some patients with related urogenital abnormalities, such as unilateral renal agenesis (as part of the Mayer–Küster–Hauser–Rokitansky syndrome) [32, 33]. Rarely, no explanation for its absence will be identifiable.

If, during orchidopexy, no vas deferens is visible during dissection of the PV and mobilisation of the cord, the following procedure is appropriate:

1. Re-examine the cord and the PV (by both observation and palpation) for evidence of the vas deferens.
2. Inspect the termination of the cord to identify the epididymis and trace it proximally to locate the epididymal end of the vas deferens.
3. Inspect the cord at the internal ring, and look for the vas deferens coursing in the extraperitoneal space medially around the inferior epigastric vessels on its way to the base of the bladder.
4. If there is still no evidence of the vas deferens, the hernial sac/PV, once separated from the vessels and divided, should be sent for histological examination for evidence of a vas deferens—or to confirm its absence. Also, the testis should be examined to determine if the epididymis is normal: in CF the head of the epididymis is normal but the body and tail of the epididymis are absent.
5. Postoperatively, a sweat test should be obtained to exclude CF, the most common cause of bilateral absent vasa. Gene screening to identify mutations in the CF

gene also should be done as many males have a mutation without the clinical phenotype of CF [34, 35].

6. A renal ultrasound may demonstrate ipsilateral renal agenesis, consistent with Mayer–Küster–Hauser–Rokitansky syndrome in a male [32, 33].

What should be done about the testis? If the testis appears normal, it would be reasonable to complete the orchidopexy, for it will fulfil its role in providing hormones, still fill the scrotum from a cosmetic point of view, and, if the contralateral testis is in a similar predicament, may serve an important role in fertility, dependent on the future development of the relevant technology.

8.3.4 Persistent Müllerian Duct Structures

A very rare syndrome that presents as UDT is persistent Müllerian duct syndrome, in which the gene for anti-Müllerian hormone (AMH) (also known as MIS or Müllerian-inhibiting substance) or its receptor is mutated. This leads to lack of the normal action of AMH with failure of the Müllerian ducts to regress and no shortening of the gubernacular cord despite normal INSL3-mediated gubernacular swelling reaction and androgen-mediated masculinisation of the external genitalia and the Wolffian duct. The affected infant has a male external phenotype with UDT and may come to surgical attention because of an inguinal hernia containing the testis. At operation, the surprised surgeon finds one or two testes with a normal spermatic cord adjacent to an infantile uterus and fallopian tubes [36, 37] (see Fig. 2.9).

The best management of this unexpected condition is to photograph the anatomy and biopsy the gonads and Müllerian ducts to confirm the diagnosis, followed by secondary partial excision of the Müllerian ducts and orchidopexy, but only after consultation with the regional DSD multidisciplinary team. Extreme care is required during excision to avoid damage to the vas deferens, as it often runs in the lateral wall of the infantile uterus. Both testes may be brought down through the same inguinal canal, if required. Although there are alleged to be some men with this abnormality who are fertile, the fact that the vas deferens enters the fornix of an infantile vagina, and that the seminal vesicles are probably absent, would suggest that a normal ejaculate is unlikely.

8.4 Spermatic Cord of Inadequate Length

8.4.1 Prentiss Manoeuvre

After mobilisation of the vas and vessels off the PV, the spermatic cord is usually of adequate length in a standard orchidopexy. However, if not the first manoeuvre is to enlarge the internal inguinal ring on its lateral side and then to continue the dissection into the retroperitoneum to free up the lateral fascial bands attaching to the testicular vessels. Then the inferior epigastric vessels are isolated by placing a right-angle forceps behind them through the back wall of the inguinal canal. The space created may be adequate to allow the testis to be brought medial to the vessels without their division, although formal transfixion, ligation, and division of the vessels enable better medial mobilisation of the vas deferens. The Prentiss manoeuvre increases the effective length of the spermatic cord by an average of 1 cm in most children [25].

8.4.2 Two-Stage Orchidopexy

A short spermatic cord is most likely to be a problem with testes in the inguinal canal or abdomen (Fig. 8.13), where either the vas or testicular vessels may be too short to reach to the scrotum. When the testis is fully mobilised and brought as far down towards the scrotum as possible, but falls short of a satisfactory position, even after a Prentiss manoeuvre, a second-stage orchidopexy becomes necessary. The testis is anchored as far distally as possible, and ≥6 months later, a second procedure is performed. Adhesions in the region of the testis and internal inguinal ring may make subsequent mobilisation of the cord difficult and hazardous, with potential risk of injury to the testicular vessels and vas deferens [38, 39].

It is generally accepted that if a high retroperitoneal dissection has been done and the testis cannot be brought into the scrotum, a staged orchidopexy is preferable to a Fowler–Stephens orchidopexy, because many of the collateral vessels which preserve the testis after testicular artery transection have been intentionally divided in the course of the retroperitoneal dissection [40].

Not all surgeons accept that the spermatic cord lengthens after the first exploration [41] or that the procedure is successful [42]. This is based on the observation of dense fibrous tissue surrounding the cord preventing further lengthening and that there is no demand placed on the testicular artery for it to lengthen [41].

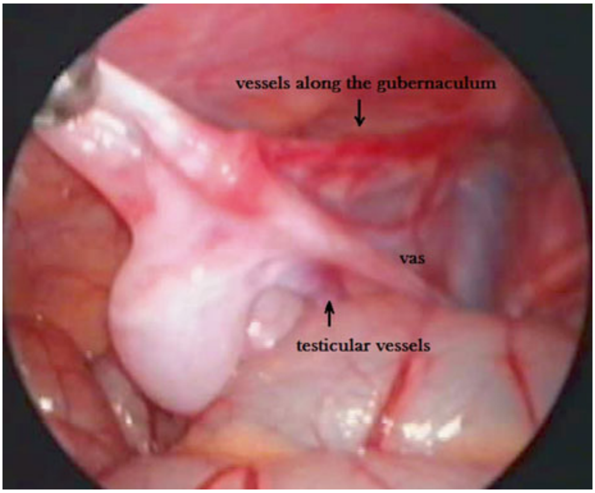

Fig. 8.13 Intra-abdominal testis seen at laparoscopy. The testicular vessels and the collateral vessels in the gubernaculum are arrowed, and the vas deferens is visible

The success rate of staged orchidopexy has been 70–90 % [39, 43] which may be better than that achieved with the Fowler–Stephens procedure.

8.4.3 Fowler–Stephens Orchidopexy

Orchidopexy involving transection of the testicular artery was advocated in 1903 by Bevan but discouraged from 1929 because of poor results [44].

Fowler and Stephens revived the procedure in 1959 after they demonstrated by intraoperative arteriography that collateral arterial vessels run along the vas deferens [45]. From these observations, they derived the 'Fowler–Stephens' orchidopexy. In this operation, the testicular artery is divided on the assumption that the testis will retain an adequate blood supply from the artery of the vas (as well as cremasteric vascular anastomoses) and that it is the testicular (also known as the spermatic or gonadal) artery which is the limiting factor in preventing an orchidopexy. The operation relies on the collateral vessels in the spermatic cord not having been disturbed; otherwise, division of the testicular artery is likely to result in testicular ischaemia and atrophy.

In the series of 17 testes treated by a Fowler–Stephens orchidopexy and reported by Gibbons et al. [46], 5 atrophied, 4 of whom had prune belly syndrome. Gibbons et al. [46] attributed these early failures with the one-stage Fowler–Stephens technique to:

1. Failure to leave a broad pedicle or tongue of vascularised visceral peritoneum overlying the vas
2. Attempting to salvage a scrotal placement after extensive cord mobilisation and dissection
3. Division of the testicular artery too close to the testis, possibly compromising the vasal collateral support
4. Direct injury to the artery of the vas and the cremasteric vessels

They added that a further contraindication to vascular pedicle division was segmental vas atresia or a detached epididymis, as there is uncertainty that there would be an adequate collateral vascular supply.

The key to the success of the one-stage Fowler–Stephens orchidopexy (at an open operation) is prior recognition of when division of the testicular artery may be necessary, so that critical dissection near the artery to the vas can be avoided, as this may compromise the collateral vasal–arterial supply [40] and is thus a contraindication to testicular vessel transection.

8.4.4 Two-Stage Fowler–Stephens Orchidopexy

The Fowler–Stephens procedure has been known for over 50 years [45] but required modification before it was to become popular as a laparoscopic procedure, particularly as a staged operation. In the first stage, the testicular vessels are ligated to allow the development of a collateral circulation. The subsequent orchidopexy is performed 6–12 months later, although it may be possible to reoperate sooner. At the second operation the artery to the vas (deferential artery) will have enlarged considerably. The 2-stage Fowler–Stephens procedure is now one of the standard options for high intra-abdominal testes on laparoscopy, as the testicular vessels can be divided far enough away from the testis to preserve the collateral anastomoses around the testis (see below).

8.4.5 Laparoscopic Orchidopexy (Impalpable Testes)

The management of the impalpable testis changed dramatically with the advent of laparoscopy [47]. Currently, there is consensus that infants with impalpable testes should have diagnostic laparoscopy, followed by either 1-stage laparoscopic orchidopexy or the division of the testicular vessels as the first stage of a 2-stage Fowler–Stephens orchidopexy. Parents also should be warned about the possibility of the vanishing testis, especially if the contralateral descended testis is larger than normal (using the rule of thumb that a normal testis is roughly the same size as the glans penis—when it is larger than the glans, it has probably undergone compensatory hypertrophy in response to loss of the impalpable testis).

Under anaesthesia at the beginning of the operation, it is prudent to perform a detailed physical examination of the scrotum and groin in search of the UDT or an atrophic nubbin. In addition the external ring should be palpated to determine whether it is open (suggesting the testis may be canalicular) or closed (suggesting the testis is intra-abdominal or ‘vanishing’). If the vas deferens can be palpated exiting from the external ring, then some surgeons would open the scrotum to find the presumed atrophic testis, which is often a tiny nubbin the size of a wheat seed. Under histology there may be haemosiderin and/or calcification.

When there is no evidence of any genital structures at the external ring or in the scrotum, then laparoscopy is the next step. An umbilical port is inserted for a 5 mm telescope so that the ipsilateral inguinal ring can be visualised from the inside. An intra-abdominal testis is usually found close to the internal inguinal ring on its short mesorchium (Fig. 8.14). Tilting the operating table head down may facilitate examination of the internal ring and environs, searching for an obvious gonad. Through lateral abdominal stab incisions (with or without 3 mm or 5 mm ports), graspers are introduced to hold the testis and to see if it can be pulled to the opposite internal inguinal ring. If this is possible, then there should be enough length of the testicular vessels for an orchidopexy without them needing to be divided (as part of a Fowler–Stephens procedure) (Fig. 8.15). A wide peritoneal flap is raised, shaped like a tennis racket, with the ‘bat’ around the testis, but distant enough from the head of the epididymis to preserve any collateral vessels between the testicular vessels and the artery to the vas (Fig. 8.16). Care needs to be taken cranially over the testicular vessels themselves and caudally over the vas, to ensure no injury to either structure as the testis, along with its adjacent peritoneum, is mobilised (Fig. 8.17).

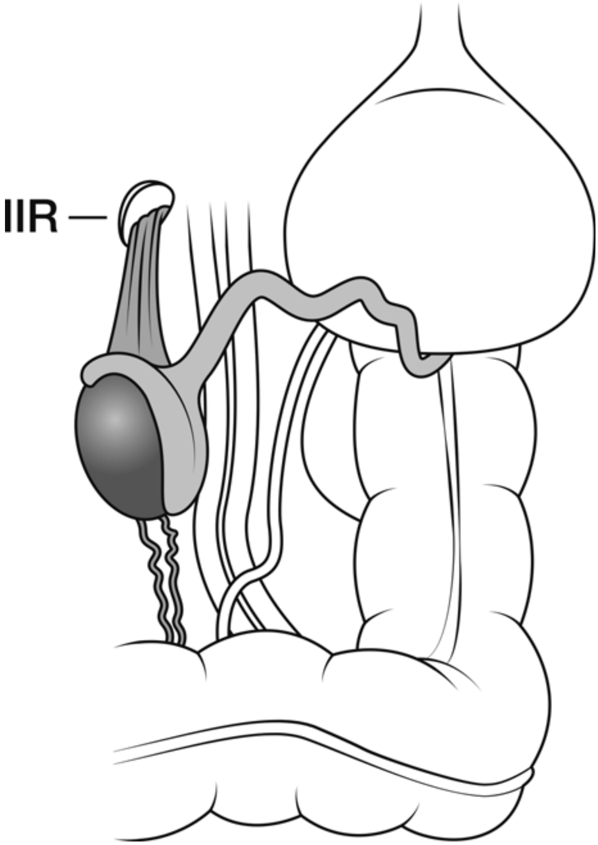

Fig. 8.14 The intra-abdominal testis is usually close to the internal inguinal ring (*IIR*)

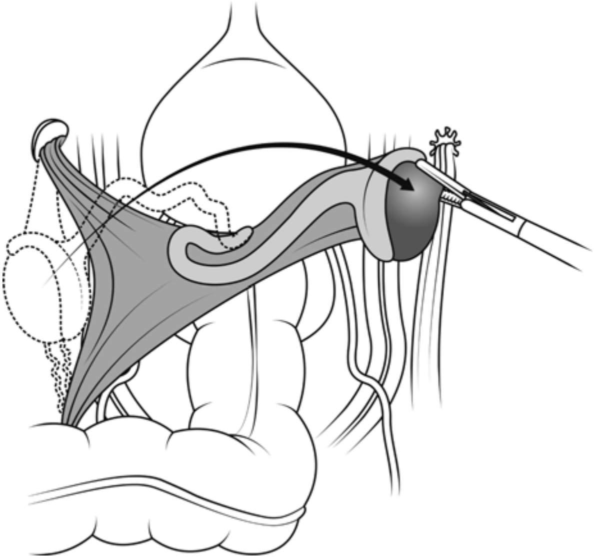

Fig. 8.15 The testis is pulled to the opposite inguinal ring to gauge how much mobility there is in its mesorchium

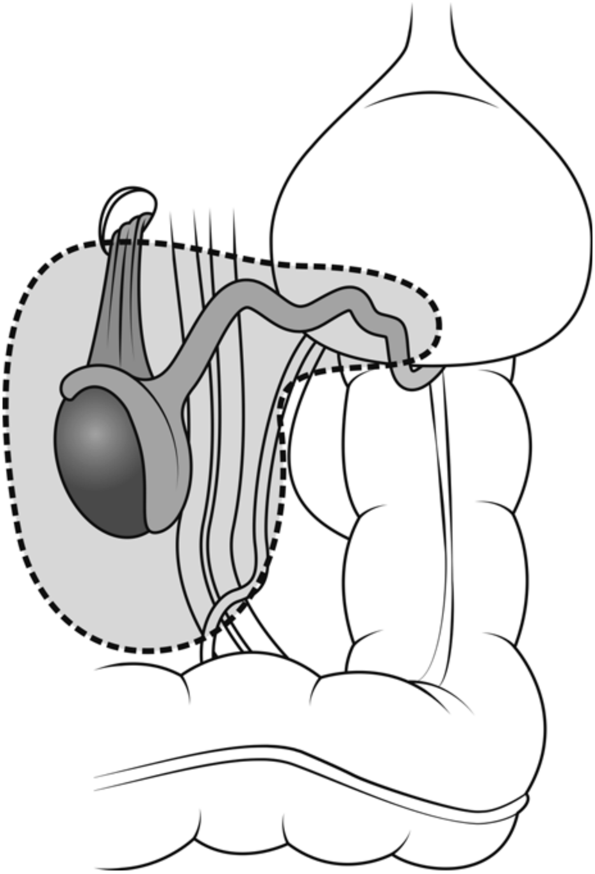

Fig. 8.16 Creating a peritoneal flap the shape of a tennis racket to preserve any collateral vessels around the testis and epididymis

A small scrotal incision is made and a laparoscopic grasper inserted up to the pubic region after preliminary blunt dissection. By careful palpation, and under vision from inside, the grasper is pushed through the external inguinal ring and through the back wall of the inguinal canal, medial to the inferior epigastric vessels and lateral to the lateral umbilical ligament (obliterated umbilical artery) and bladder. The mobilised testis is then pulled down to the scrotum and anchored there with a suture, similar to a standard orchidopexy. Any intra-abdominal fascial bands limiting the vessels and/or vas are carefully divided under vision. Closure of the new ‘inguinal canal’ is not needed.

If the testis was found further away from the internal ring, the ipsilateral colon is mobilised to expose the proximal gonadal vessels to enable the first stage of a 2-stage Fowler–Stephens procedure. The testicular vessels are tied or clamped far enough away from the epididymis to preserve any peri-gonadal collaterals (Fig. 8.18), as the remaining blood supply to the testis will adapt by dilatation, enabling orchidopexy 6–12 months later.

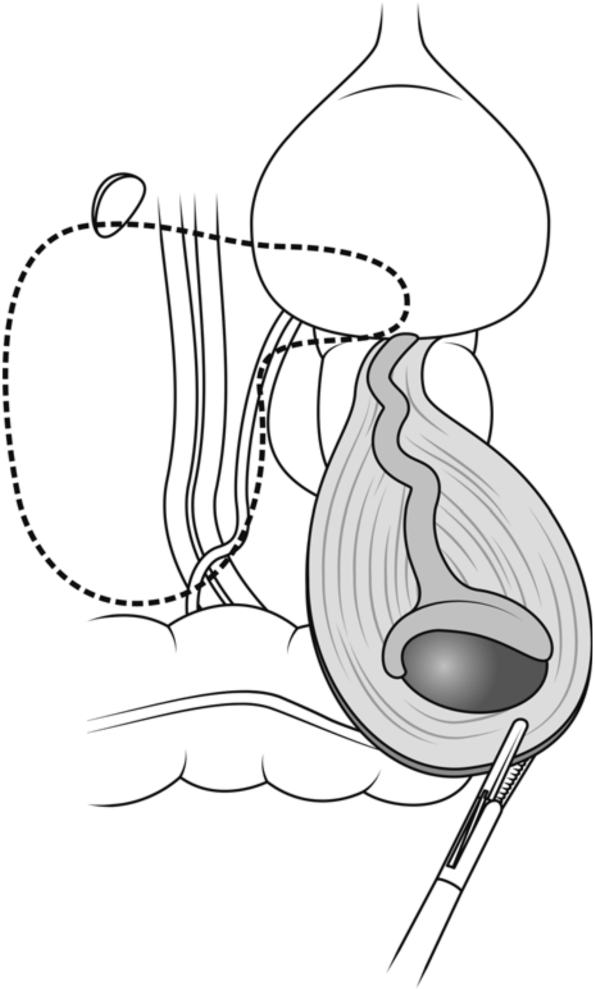

Fig. 8.17 Once the testis has been mobilised on the peritoneal flap, it can be pulled to the scrotum, often through the back wall of the inguinal canal medial to the inferior epigastric vessels, as in the Prentiss manoeuvre

After 6 months the artery to the vas will have adapted, and at repeat laparoscopy the testis can be mobilised by creating a wide peritoneal flap similarly to that described above and brought down to the scrotum after safely dividing the previously ligated testicular vessels.

Shehata [48] has recently developed an alternative to the 2-stage laparoscopic orchidopexy, by stretching the testicular vascular pedicle at the first operation, rather than dividing/ligating the vessels as in the Fowler–Stephens procedure. By pulling the testis to the opposite lateral abdominal wall and suturing it to the muscles, the vessels elongate in response to the stretching, and some months later the testis can be detached and brought to the scrotum as in the second-stage Fowler–Stephens operation. There are no follow-up studies yet to this technique, but it looks promising [49].

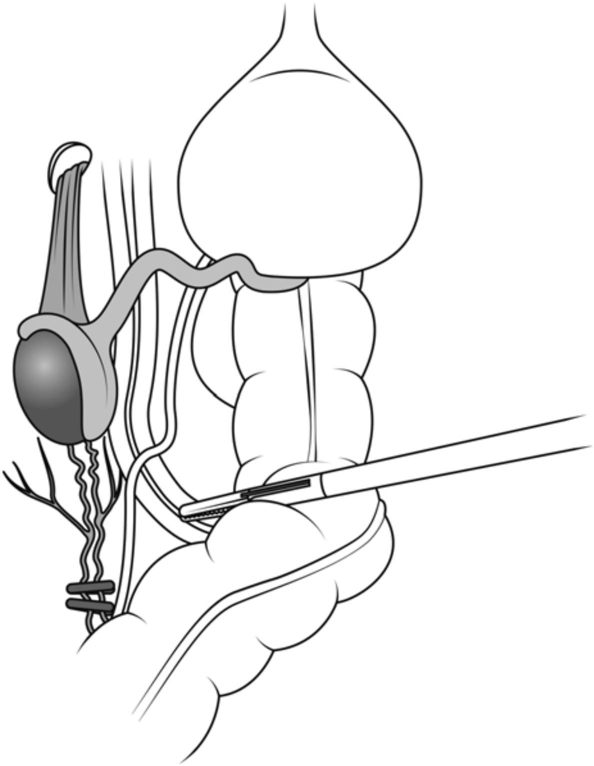

Fig. 8.18 In the 2-stage Fowler–Stephens operation, the colon is mobilised to enable the testicular vessels to be clipped or ligated far enough away from the epididymal head to avoid damage to the collateral blood supply

8.4.6 Microvascular Anastomosis (Testicular Autotransplantation)

Microvascular anastomosis with testicular autotransplantation [48, 49] is a potential option for the very high testis, but in most situations it has been superceded by the advent of laparoscopy for the high, impalpable testis. However, in a very few cases of very high intra-abdominal testes, where no significant collateral vessels along the vas or gubernacular attachment can be identified by laparoscopy, this procedure is an option.

Bianchi [50] has reported a series of 12 testes in boys, aged 3–15 years, in which a microvascular testicular anastomosis was performed, with testicular ischaemia times of 75–135 min. Arterial anastomosis failed in two (although one of these survived on the artery of the vas). The long-term results, including fertility, remain unknown. In a similar series reported by Frey and Bianchi [51], the mean age at operation was 7.4 years, with an age range of 3.25–16 years.

Smaller vessels are more difficult to anastomose, and the earlier age at which orchidopexy is now performed may limit the feasibility of the technique. The skill required for the microsurgical technique and the equipment necessary make this method unrealistic for the majority of paediatric surgeons confronted intraoperatively with an intra-abdominal testis [46].

8.4.7 Testicular Biopsy

Testicular biopsy taken at time of orchidopexy is recommended in cases with ambiguous genitalia, DSD cases, and other syndromic cryptorchidism in order to diagnose intratubular germ cell neoplasia (ITGCN), because the risk is increased in these patients. Today, modern immunohistochemical staining methods make it easier to identify ITGCN in boys more than 20 months old in standard Pathological Departments (see Sect. 6.5). Testicular biopsies taken for evaluation of the fertility potential are so far optional in centres with special interest of research within this field. A frequently asked question is whether testicular biopsies cause the production of sperm antibodies. The answer to this question is a clear 'no', as long as the biopsy is done on boys less than 10 years of age. This is about the time the Sertoli cells mature and begin to generate the blood–testis barrier to protect the developing spermatids, as they are potentially antigenic. Prior to this only primary spermatocytes are present which are not antigenic. Follow-up studies confirm that prepubertal testicular biopsies do not produce antisperm antibodies in adulthood [52, 53].

At orchidopexy when the tunica albuginea is exposed, a small incision of about 0.5 cm is made in order to obtain a biopsy of 2×2×2 mm. For assessment of ITGCN, a unique sample may carry a risk of incomplete evaluation. However, more than a single biopsy of the prepubertal testis is not feasible, owing to the small size, so the risk of a false negative should be kept in mind.

The tunica albuginea should be closed with a 4-0 absorbable suture that may also be used for fixation of the testis.

8.5 The Unilateral Impalpable Testis

In the case of the boy who presents with a unilateral impalpable testis (with compensatory hypertrophy of the contralateral testis), the parents should be counselled prior to surgery that there is a greater than 50 % chance that the testis will be absent or be appropriately removed [54]. Despite the fact that a unilateral impalpable testis is twice as common on the left, the outcome is similar on both sides.

8.6 Surgical Management in the Post-pubertal Child

The management of the post-pubertal cryptorchid testis is based on an estimation of the risk of death from a germ cell testicular tumour against the risk of death from orchidectomy [55, 56]. Based on a 0.04 % incidence of germ cell tumours in cryptorchid patients in 1985 [53] and the fact that 68 % occur in the 15–35-year-old age group, it was found that the risk of surgery begins to outweigh the risk of deaths from germ cell testicular tumours at 32–34 years.

8.7 Indications for Orchidectomy

The indications for orchidectomy, rather than orchidopexy, for UDT are listed in Table 8.1, although the exact applications may be disputed.

Most clinicians would accept that if the UDT has persisted through puberty and is small or dysgenetic with a normal or hypertrophied, fully descended contralateral testis, orchidectomy is the treatment of choice [57]. This is especially true if the UDT is high.

8.8 Complications

The most significant complication of orchidopexy results from operative injury to the testicular vessels during separation of the hernial sac and mobilisation of the cord (Table 8.2).

The testicular vessels are closely applied to the PV: inadvertent damage to the testicular artery may render the testis ischaemic and lead to its atrophy in the months following surgery. This will be evident clinically when the testis seems to ‘disappear’.

There is no evidence that early orchidopexy is associated with an increased risk of vascular damage or subsequent testis atrophy [57] although such data come from paediatric surgical centres and have been disrupted recently (see Chap. 10.2). It may well be that there is a higher attrition rate when the procedure is done at an early age by a general surgeon, who is unlikely to use loupe magnification. Even paediatric surgeons acknowledge a 2 % incidence of testicular atrophy after hernia repair (without UDT) in infancy [57, 58]. The other potential case for subsequent testicular atrophy is excessive tension on the cord which compromises blood flow through the testicular artery. Atrophy of the testis is most commonly seen when abdominal testes are brought into the scrotum or when the Fowler–Stephens procedure has been employed [57]. The testis seldom becomes atrophic when brought into the scrotum without tension.

The high intracanalicular or intra-abdominal testis on a short cord may be difficult to bring down into the scrotum and either may be fixed in the scrotum under tension (upward retraction) or brought only as far as the neck of the scrotum—later requiring a second procedure to bring it fully into the scrotum. In the former

Table 8.1 Indications for orchidectomy rather than orchidopexy

1.	Unilateral cryptorchidism in post-pubertal male if testis is:
	Small or dysgenetic or very high
	Contralateral testis fully descended and normal or hypertrophied
2.	? Small dysgenetic testis at any age if contralateral testis descended
3.	? Inability to bring testis into scrotum
4.	? Adult with cryptorchidism

Table 8.2 Complications of orchidopexy

1.	Testicular atrophy	Injury to testicular vessels	
2.	Testis not fully descended	Never reached the scrotum	(a) Fully mobilised cord too short
			(b) Inadequate mobilisation
		Retracted out of scrotum	(a) Excessive tension on cord
			(b) Inadequate fixation in scrotum
3.	Transection of vas deferens		
4.	Haematoma	Usually from cremasteric vessels	
5.	Infection	Usually of scrotum	
6.	Inguinal hernia	Tear in neck of peritoneum at internal ring and leaving peritoneum in continuity with PV	
7.	Torsion of testis (rare)	Inadequate fixation	

situation, the cord structures usually elongate with time and the final position of the testis is adequate. In a few patients, however, the testis adopts a position at the neck of the scrotum and requires a repeat orchidopexy. Most commonly, postoperative testicular retraction results from inadequate retroperitoneal mobilisation of the testicular artery, from failure to strip off the cremasteric muscle fibres or by failure to ligate the patent PV [24]. Testicular retraction also may occur following hydrocele or hernia repair if the testis is not returned to the scrotum at the end of the procedure.

Failure to completely separate the hernial sac from the remainder of the cord may lead to inadvertent opening of the peritoneum at the internal ring. If this is not recognised and closed during the procedure, an inguinal hernia may become apparent in the postoperative period.

Torsion of the testis following orchidopexy is a rare event, but it would seem reasonable to expect that opening the tunica vaginalis and suturing the tunica albuginea (the capsule of the testis) to the fascia of the scrotum during orchidopexy might reduce this risk.

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Hormonal Treatment

9

9.1 Historical Background

The idea that hormonal treatment might be effective in undescended testis (UDT) probably dates from the early part of the last century, when it was first appreciated that sexual development was controlled by hormones [1]. In 1928, urine of pregnant women was noted to contain a substance which stimulated the ovary and testis [2]. A few years later extracts of pregnancy urine were used to treat adolescents and young men with hypogonadism and UDT [3].

In 1932, Engle induced descent of the testes experimentally in the macaque monkey by administering hormone extracts from the anterior pituitary and pregnancy urine. These early studies in Germany and America led to a large number of clinical trials of hormonal extracts containing anterior pituitary hormones, which demonstrated induction of testicular descent at widely varying rates [4]. As the years passed, purified human chorionic gonadotrophin (hCG) became available and for many years was a standard treatment for UDT in many parts of the world. Success rates with this substance varied enormously [5]. Intranasal treatment with gonadotrophin releasing hormone (GnRH) was first used in 1974 [6]. Since then, hCG and GnRH hormonal treatment have been advocated with varying enthusiasm over the years. It is interesting to reflect that testicular descent in the macaque monkey is slightly different from the human (Chap. 1), and before sexual maturity the testis occupies an inguinal position similar to an ascending testis in humans. It is no surprise, therefore, that gonadotrophins trigger testicular 'descent' in the monkey.

9.2 Rationale for Treatment

Hormonal treatment is based on the controversial hypothesis that the hypothalamic-pituitary–gonadal axis is deficient in the majority of infants with UDT. Empirical evidence from the earlier studies in the 1930s led to the simplistic idea that androgen deficiency caused UDT, and therefore hormonal stimulation of androgen

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production would induce testicular descent. Androgen itself was abandoned as a form of treatment because of the side effects of precocious puberty. However, it was believed that hCG or GnRH would stimulate local production of testosterone sufficient to induce descent without causing such high elevation in serum testosterone that the unpleasant side effects were produced.

9.3 Efficacy of Hormonal Treatment of Cryptorchidism

Great variation of the effects of hormonal treatment has been reported, with success rates from 0 % to 55 % with hCG and 9 % to 78 % with GnRH, depending partly on different inclusion criteria [7, 8]. Cryptorchidism has also been treated with synthetic analogues of GnRH [9–11] and combined hormonal therapy [12–18]. Pyorala [18] reviewed 33 studies using hormonal therapy for cryptorchidism from 1975 to 1990. In the meta-analysis of the nine randomised controlled trials available, hormonal therapy was effective in approximately only a fifth of the cases; GnRH 21 % (CI 18–24 %), hCG 19 % (CI 13–25 %), and placebo 4 % (CI 2–6 %). If retractile testes were excluded, the success rate of GnRH was even lower: 12 % (95 % confidence interval 8–15 %). In long-term follow-up, 24 % (CI 13–35 %) of the testes that descended after GnRH treatment had relapsed. Subgroup analysis of results based on the initial position of the testes found a greater success rate the more caudal the position of the testes was before treatment. The authors also mentioned that the age of the boy may play a role in the success rates obtained with hormonal treatment.

Reports on the optimal age for hormonal treatment of UDT are not conclusive [8]. Early studies concluded that the result was very poor at ages less than 4 years [19]. Cortes et al. [20] also found no response to hormonal treatment before the age of 4 years. De Muinck Keizer-Schrama and Hazebroek [19] found the highest success rates with GnRH in the 5–12-year age group (Fig. 9.1). This result was somewhat in contrast to other studies [21, 22] in which the highest success rate was achieved in boys aged 2–5 years. In a study of bilateral cryptorchidism, Christiansen et al. [23] found that both hCG and GnRH were more efficient in younger boys. However, in the meta-analysis of the results of pooled data for uni- and bilateral cases, there was no significant difference in efficacy between patients older or less than 4 years [18, 24]. Henna et al. [24] reviewed all randomised trials until June 2003, adding three trials to the nine reviewed by Pyorala et al. [18]. A meta-analysis on two randomised controlled trials comparing hCG versus GnRH reported success rates of 25 % and 18 %, respectively. Meta-analysis of nine randomised controlled trials comparing GnRH with placebo showed success rates of 19 % and 5 %, respectively. Ong et al. [25] summarised randomised and nonrandomised trials published from 1991 to 2003. The overall success rates reported by the six randomised, controlled trials ranged from 8 % to 43 %. The studies generally agree with Pyorala et al. [18] in that therapeutic success is greater when the testis is in a lower position and age is not an important determinant for success. Four trials reported that hormonal therapy is more effective in bilateral cases. Although the efficacy of hormone

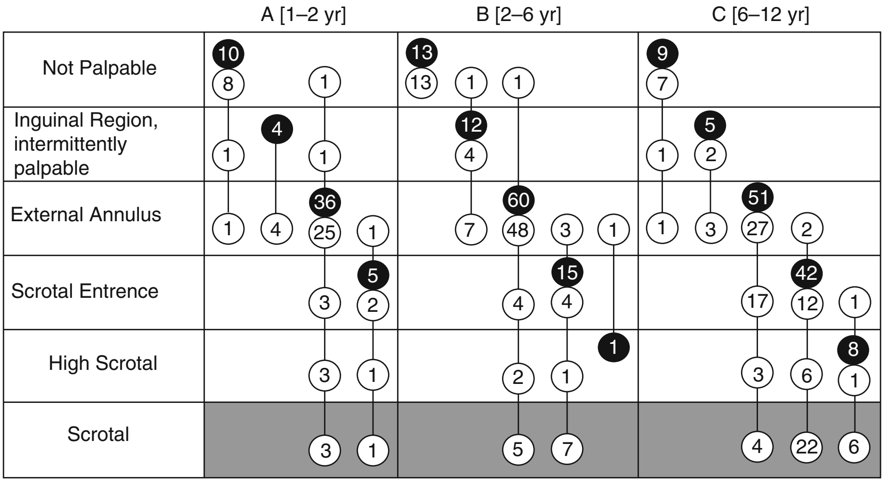

Fig. 9.1 The most caudal position of the testis (indicated by the number of testes) before (●) and after (O) LHRH treatment intranasally (excluding placebo descents). These results are from the double-blind, placebo-controlled trial of LHRH nasal spray performed by de Muinck Keizer-Schrama et al. [30] and are reproduced with permission of authors and publisher

treatment is very moderate, it is better than nothing [8]. The results of hormonal treatment in controlled, randomised studies are summarised in Table 9.1. During the last decade no controlled, randomised hormonal studies to induce testicular descent have been carried out. However, hormonal therapy is used for that purpose mainly in areas of central Europe. Recently neoadjuvant hCG therapy was shown to induce testicular descent to the scrotum in 44.5 % of 229 UDT in 204 cryptorchid boys from Poland [26].

9.4 Standard Regimens

A number of different administration regimes have been proposed for hCG treatment of boys with UDT. They range from 100 I.U. per kg at 4–5-day intervals for 4 weeks [27] to 1,000 I.U. weekly for 2 weeks [16]. Christiansen et al. [23] administered hCG twice a week for 3 weeks using 100 I.U. per kg up to a maximum of 1,500 I.U. Saggese et al. [16] gave FSH (simultaneously with hCG) in a dose of 75 I.U. weekly for 6 weeks, but found that the addition of FSH made little appreciable difference to the results.

The dose regime for LHRH is reasonably standardised: it is usually given in a spray with 100 mcg in each nostril six times a day for 4 weeks. Alternative regimes administer 200 mcg to each nostril three times a day [7, 10, 28–31]. Apart from intranasal spray, the other method of LHRH administration tried was pulsatile–intravenous injection using a portable syringe pump [32]. LHRH was administered in doses of 10–100 mcg per day given in a 3 min pulse every hour for 3–19 weeks.

Table 9.1 Results of trials of LHRH treatment

Study	Retractile testis included	Treatment groups	No patients (testes)	Success rate (%)	Relapse rate (%)	Age—years
Illeg et al. (1977)	No	Total	84 (112)			1.5–12
		LHRH	46 (61)	38		
		Placebo	38 (51)	2		
Hagberg and Westphal (1992)	No	Total	47 (61)		22	2–10
		LHRH	23 (29)	40		
		Placebo	24 (32)	3		
Karpe et al. (1985)	No	Total	50 (5)		12	3–8
		LHRH				
		Placebo				
Klidjian et al. (1985)	No	Total	40 (54)			2.5–11
		LHRH	22 (29)	14		
		Placebo	18 (25)	0		
De Muinck Keizer-Schrama (1986)	No	Total	237 (281)			1–12
		LHRH	(151)	9		
		Placebo	(130)	8		
Rajfer et al. (1986)	No	Total	33 (37)			1–5
		LHRH	16	19		
		Placebo	14	6		
Wit et al. (1986)	No	Total	49 (70)			1.5–12
		LHRH	(35)	17		
		Placebo	(35)	0		
Bertelsen et al. (1987)	No	Total	46 (69)		13	5–12
		LHRH	23 (34)	26		
		Placebo	23 (35)	4		
Hagberg and Westphal (1987)	No	Total	37 (42)		42	0.5–3.5
		LHRH	17 (19)	37		
		Placebo	20 (23)	9		
Hocht (1987)	No	Total	60		12	1–9
		LHRH	30	57		
		Placebo	30			
Olsen et al. (1992)	No	Total	123	8		2–12
		LHRH	63	10		
		Placebo	61	2		
Bica et al. (1992)	No	Total	59		1	1–8
		GnRG + HCG	22 (25)	36		
		Placebo _ HCG	19 (19)	10		
		Surgery	18 (21)	–		

Table 9.1 (continued)

Study	Retractile testis included	Treatment groups	No patients (testes)	Success rate (%)		Relapse rate (%)	Age—years
Christiansen et al (1992)	No	Total	257 (420)	Bilateral	Unilat	5	1.5–13
		HCG	85 (133)				
		LHRH	83 (140)	23	29		
		Placebo	89 (147)	9	0		
				2	3		
Hoorweg-Nijman (1994)	Yes	Total	22 (28)				1.5–5
		FSH-HCG	14 (18)	33			
		Placebo + HCG	8 (10)	60			
Bertelloni et al. (2001)	Yes	Total	155				1–4
		HCG	37	19			
		HCG-HMG	39	13			
		GnRG	39	13			
		GnRH + HCG	40	15			
Esposito et al. (2003)	Yes	Total	324 (418)				0.5–13
		HCG	113	35			
		HMG	35	0			
		LHRH	85	29			
		HCG-HMG	27	26			
		LHRH + HCG	64	30			
		Placebo					

A battery-operated, programmable syringe driver was used with a daily insertion of the scalp vein needle into a vein on the anterior abdominal wall. The needle was changed daily by the parents. This complex regime was developed in an attempt to simulate natural hypothalamic secretion rather than to follow the pharmacological approach used by others [32]. It has since been abandoned because this degree of intervention was not well tolerated by the patients and the results were poor.

9.5 Possible Benefits of Hormonal Treatment

The advantage of hormonal therapy would appear to be in distinguishing UDT from retractile or ascending testes. Retractile or ascending testes respond by descent almost uniformly, in contrast to intracanalicular or impalpable testes that almost never respond to treatment. Many authors have suggested, therefore, that hormonal therapy could be used to distinguish ascending or retractile testes from congenital UDT [33].

Hadziselimovic et al. [34] have suggested that hormonal therapy may have a further role in stimulating testicular physiology to restore the normal function of the testes after surgery. They biopsied 15 of 31 testes which failed to descend in response to hormone treatment and required orchidopexy [34]. LHRH therapy caused a marked increase in the size of the Leydig cells and in their content of endoplasmic reticulum, suggesting a recruitment of precursor Leydig cells from fibroblasts. In addition, they have suggested that the number of germ cells per tubule may be increased after LHRH therapy, independent of the need for surgical treatment. In other words, they have proposed that even though surgery may be required to relocate the UDT into the scrotum, hormone treatment may be needed in addition to stimulate normal germ cell maturation. Su et al. [35] studied testicular histology of 30 patients with undervirilisation syndromes. They found that gonocytes were present in 15/16 patients under 2 years old. Spermatogonial stem cells were present in 25/30 patients. With increasing age, the mean number of spermatogonial stem cells per tubular transverse section decreased from ~4 to 0, and gonocytes per tubular transverse section decreased from ~1.5 to 0. Spermatogonial stem cells were present in CAIS and PAIS patients at 1.5 and 3.5 weeks old, respectively. They concluded that gonocytes may transform into spermatogonial stem cells earlier than expected in patients with undervirilisation syndromes. Lack of androgens may stimulate other non-androgenic regulators to trigger transformation. This study does not exclude the possibility that gonadotrophin stimulation has a role in germ cell maturation. Insufficient work has been done so far on the effect of hormone treatment on fertility, making it difficult at present to evaluate this hypothesis. However, the idea that the position of the testes and their physiology may need separate treatment needs careful consideration.

9.6 Why Hormonal Treatment Fails

De Muinck Keizer-Schrama et al. [36] investigated the anatomical reasons for failure of LHRH hormonal therapy. After two courses of LHRH nasal spray, 48 out of 281 testes (18 %) in 237 prepubertal boys had undergone full descent into the scrotum. Of the unsuccessfully treated boys, 170 subsequently had orchidopexy for 196 persistent UDT. At operation, anatomical abnormalities that were believed to account for the failure of hormone treatment were found in 80 % of children. Hazebroek et al. [37] found the most common abnormality to be failure of the processus vaginalis to extend beyond the level of the pubic bone. In addition, these testes were often associated with major epididymal abnormalities or a persistence of a patent PV. In a small number of children, the surgeon noted an abnormal attachment of Scarpa's fascia obliterating the entrance to the scrotum. This study is consistent with many others which together suggest that in ectopic testicular descent or in the testis in which a presumed mechanical abnormality is present (e.g. obstruction at the neck of the scrotum) the response to hormone treatment is poor.

9.7 Adjunctive Therapy

Hadziselimovic and Herzog reported in 1997 that the luteinising hormone-releasing hormone analogue, Buserelin, administered intranasally every other day for 6 months following successful orchidopexy, appears to have a long-lasting, positive effect on germ cells. In another study, Huff et al. [38] reported that GnRH treatment after orchidopexy improved total germ cell counts in 75 % of the patients. These results have partly been confirmed by other groups. In a study by Lala et al. [39] with pre-orchidopexy GnRH 1.2 mg per day for 4 weeks and 500 I.U. HCG 3 × per week for 3 weeks in 52 cases versus 30 orchidopexy only, they found normal germ cell count per tubule in 62 % of cases and 23 % of controls. Similarly, Schwentner et al. [40] gave intranasal GnRH 1.2 mg per day for 4 weeks preoperatively in 21 cases versus orchidopexy only in 21 controls. The mean number of spermatogonia per tubule was 1.11 in unilateral and 0.96 in bilateral cases versus 0.47 and 0.56, respectively, in controls. Jallerili et al. [41] prospectively assigned a total of 24 boys, 12–123 months old (median 34.5), with 24 UDT into two groups during a 24-month period. The patients were randomised to receive either orchidopexy alone ($n=12$) or orchidopexy combined with neoadjuvant GnRH therapy ($n=12$) as a nasal spray for 4 weeks at 1.2 mg/day. In both groups, testicular biopsies were performed at orchidopexy, and the histopathologic fertility index was determined.

The mean fertility index in the group treated with GnRH before surgery was significantly greater (0.88 ± 0.31) than in the group without hormonal stimulation (0.49 ± 0.52; $P=0.02$). Zivkovic et al. [42] also found that hormonal therapy improved the histopathology of the abnormal contralateral descended testis in unilateral cryptorchidism without harming the germ cells. So adjuvant hormonal therapy with gonadotrophins may have a positive effect on germ cell maturation (Fig. 9.2); however the exact mechanism of action is not known and further controlled studies are needed in order to select the right candidates for treatment and prove the long-term effect (see Chap. 6). Chua et al. supported these statements in a recent published meta-analysis on studies using gonadotrophin-releasing hormone for improvement of fertility index among children with cryptorchidism [43].

9.8 Side Effects of Hormonal Treatment

It has generally been assumed that the adverse effects of hormonal treatment are few and transient, and only included erections, growth of the penis, pain in the genital region and injection sites, and psychological changes [23]. However, during recent years, accumulating evidence of deleterious effect on the germ cells has been described. Thus, several authors [44–46] reported that hCG treatment before orchidopexy in prepubertal boys induced apoptotic changes in the germ cells and inflammatory changes in the testes, not seen in those who underwent surgery without prior hCG treatment. Furthermore, Dunkel et al. [47] demonstrated that treatment with hCG for cryptorchidism is followed by an increase in germ cell apoptosis. The degree of apoptosis correlated negatively with the testis volume and positively with

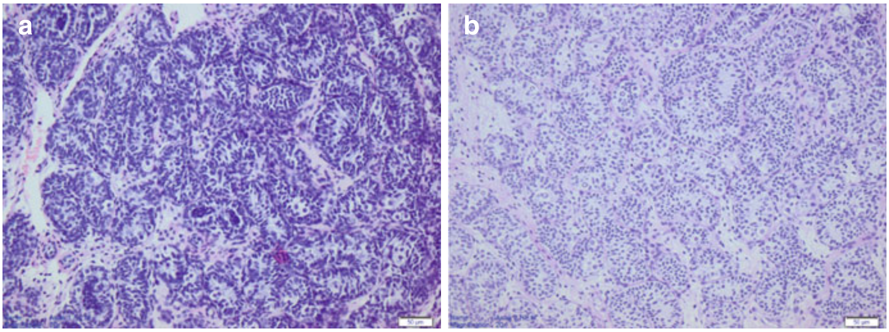

Fig. 9.2 (**a**) Testicular histology in a 9-month-old boy at time of orchidopexy for bilateral cryptorchidism. The number of germ cells per tubular transverse section was decreased (in average 0.05 germ cells per tubule). There are no adult dark spermatogonia present. Despite this there was no reactive increase of FSH and LH (0.5 I.U./l and 0.1 I.U./l respectively). (**b**) Testicular histology in the same testis at re-biopsy 1 year later, after 4 months of LHRH treatment (400 µg every second day). The number of germ cells per tubular transverse section is now normalised. Some germ cells have transformed into adult dark spermatogonia. In the nuclei a vacuole is observed which appears in the sections as a circular light area

serum levels of FSH 20 years later, in adulthood. Similarly, Cortes et al. [20] found that hCG or GnRH treatment before surgery in 1–3-year-old boys suppressed the number of germ cells, compared to those undergoing surgery alone.

Conclusions

Hormone treatment for UDT has been tried for around 80 years with very limited success. Initial enthusiastic reports, first with androgens, then hCG and finally LHRH, have been replaced by subsequent poor results. It is now well established that hCG and LHRH therapy to achieve testicular descent have no significant place in patients with congenital cryptorchidism. Their potential role in the management of ascending or pathologically retractile testes, however, remains controversial. They may become useful ways to diagnose these apparently acquired anomalies. LHRH treatment may be important as an adjunct to surgery to stimulate germ cell maturation and hence reverse the potential infertility of maldescended testes after orchidopexy.

At present, hormone treatment should be reserved for those institutions carrying out controlled trials and cannot be recommended for general use. In some older children, where there is a strong likelihood of the high testis being ‘retractile’ or ‘ascending’, hormone therapy may confirm the diagnosis and avoid surgery. LHRH treatment would seem superior to hCG administration, if only because a series of painful injections can be avoided.

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Results of Treatment

10

10.1 Criteria of Assessment

The results of treatment of undescended testis (UDT) can be assessed at several different levels. In some boys the cosmetic appearance will be the important factor, while for others the potential for fertility is of prime importance. The risk of malignancy during young adult years is less critical initially, but becomes more important with age.

10.2 Cosmetic Result

Surgical correction of an UDT will result in an intrascrotal testis of reasonable size in a very high percentage of children. In short-term results success of treatment is most often defined as a testis that postoperatively remains in a satisfactory scrotal position without atrophy [1]. The success rate in proportion of atrophy and recurrent cryptorchidism in childhood cannot be estimated until follow-up 1 year postoperatively. Few studies are dealing with the results of surgery in retractile or ascending testes, but clinical operative results should be excellent in these cases as the testes had previously shown the potential to reach a scrotal position. Clarnette et al. [2] found a 100 % success rate in a small series of 25 orchidopexies in ascended testes with an age of 4–13 years at time of surgery.

In congenital cryptorchidism the trend is towards earlier surgical correction (6–12 months of age) to prevent development of male infertility [3, 4]. However in larger published series of orchidopexies the median and mean age is still more often 3 years or more. The overall success rate of orchidopexy for inguinal testes at the level of external annular ring is expected to be around 90 % [5].

In a previous meta-analysis of 64 studies in 8,425 cryptorchid testes, Docimo [6] reported the following success rates: 92 % for testes that were originally distal to the external annular ring and 87 % for 'true' inguinal testicles (i.e. canalicular). Finally for intra-abdominal testes the reported success rate was 74 %.

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In a recent series of 24 children who had previous inguinoscrotal surgery, 19 testes reached a scrotal position, 68 % spontaneously and 32 % after repeat orchidopexy. There was no difference in the rate of spontaneous descent in those who had previous orchidopexy versus inguinal herniotomy [7].

The success rates of operative correction of abdominal and peeping testes are generally lower, but the diagnostic and therapeutic laparoscopic approach widely used during recent years may have increased the success rates. Numerous series have been published with a variety of techniques. The overall success rate of operative correction of intra-abdominal and peeping testes in 24 different series including 1,468 orchidopexies reviewed by Taran and Elder [5] has been estimated to 84 %. It is important to be aware that peeping testes are included in this figure. Furthermore, primary orchidectomised hypoplastic abdominal testes may be excluded in advance, which may influence the success rate positively.

In a meta-analysis of 61 articles on operative success of 1,405 intra-abdominal testes, Elyas et al. [8] found that single-stage Fowler–Stephens orchidopexy was discussed in 9 articles, a two-stage procedure in 36, and both approaches in 16. There were no randomised, controlled trials, and most studies were cohort or case series. The pooled estimate of success rates was 80 % for single-stage Fowler–Stephens orchidopexy (95 % CI 75–86) and 85 % for two-stage Fowler–Stephens orchidopexy (95 % CI 81–90). There was no difference in the success rate between laparoscopic and open techniques in either single- or two-stage Fowler–Stephens orchidopexy. There were no complications reported with single-stage, while ileus, haematoma, and infection were the most common complications with two-stage Fowler–Stephens orchidopexy.

However, the clinician needs to be careful in comparing the data in these series concerning inguinal testes at the level of external inguinal ring as well as series concerning the intra-abdominal and peeping testes. In both respects these series may include selected patients from surgeons specially dedicated to improve operative technique or high-volume paediatric centres. Less experienced centres or centres with inferior results are probably unlikely to report their experience [5]. So-called publication bias may in this way indicate that the aforementioned success rates represents an average maximum. However, re-do operations are not included and may increase slightly the end result, though it may be difficult surgery [1].

Generally the effect of the patient's age at time of operation is not considered to influence the success rate [6]. Excellent results have been achieved in a series of orchidopexies in 9-month-old boys [9]. However, in a study by Thorup et al. [10] including 356 boys with 418 orchidopexies and median 1 year of follow-up, they found 367 (85 %) testes were in the scrotum without iatrogenic atrophy. Eight testes were atrophied and in 43 cases a repeat operation was performed to achieve a scrotal position of the testis. All acquired UDT had a successful result. The age at operation for the group with congenital UDT in the intracanalicular position or in a position close to the external inguinal ring was 4 months to 14.5 years. In the latter group the median age at operation for the 41 failures was 2 years and 4 months, which is significantly younger than the median age for the more successful operations (3 years and 9 months). The similar trend was seen in a large series of 1,400 orchidopexies performed at the Hospital for Sick Children, Toronto, where 4.7 % ended up with postoperative atrophy [11]. The mean age of the total material of boys with orchidopexy was 5.4 years, and the median age for testicular atrophy was 4.8 years. In another study reviewing the results of 349 orchidopexies, Carson et al. [12] found no increase in testicular atrophy in patients less than 13 months. Interestingly, it has recently been shown that there is a chance of spontaneous descent of a testis with suprascrotal position after orchidopexy if re-do operation is delayed until puberty [7].

In another recent, retrospective review of 1,538 boys having orchidopexy in Scotland, 23 % had bilateral operations. The need for repeat surgery was 1.6 % over 18 years, with slightly higher failure rates when bilateral orchidopexy was performed at the same time [13].

When orchidopexy was performed by the occasional operator, it had a lower success rate than when done in high-volume specialised paediatric surgical centres, consistent with the consensus that the procedure needs dedicated surgeons [14].

At follow-up of patients in adulthood after operation for unilateral cryptorchidism in childhood, it has been shown that the operated testis most often has a higher scrotal position than the contralateral natural descended testis [15]. In many long-term follow-up studies, the size of the testis has been documented. In most series, testicular volume is found to be slightly lower than normal in adults following orchidopexy in childhood. Decrease in testicular volume is usually more marked in those men with a past history of bilateral orchidopexy [16, 17].

10.3 Fertility

10.3.1 Human Follow-up Studies

Men with a history of cryptorchidism have an increased risk of infertility. Outcomes related to infertility include the paternity rate; semen analysis; measurement of serum LH, FSH, and inhibin-B; and testicular size. It has been shown that in adults the testicular size and sperm density is positively correlated to the germ cell status in the cryptorchid testes in childhood [18, 19]. Today, operation within the first year of life is often performed in order to preserve testicular germ cell maturation [3, 4, 12].

At time of birth cryptorchid patients harbour germ cells in the testes, but as a group in reduced number compared to normal controls. From about 15 months of age germ cells may be lacking [18]. The higher the age at surgery for cryptorchidism, the higher is the risk of finding no germ cells in a testicular biopsy taken at time of surgery [20]. At the age of 11 years 35 % of the boys lack germ cells in their cryptorchid testes (Fig. 10.1). In cryptorchidism the mean number of spermatogonia and gonocytes per tubular cross-section (mean S/T) in percent of the age-specific value correlates positively with the sperm count in adulthood [20, 21]. When the S-/T-values bilaterally are normal in biopsies taken at orchidopexy for bilateral cryptorchidism, a normal sperm count is expected in adulthood. If decreased mean S-/T-values are found, the risk of later infertility is high and related to the

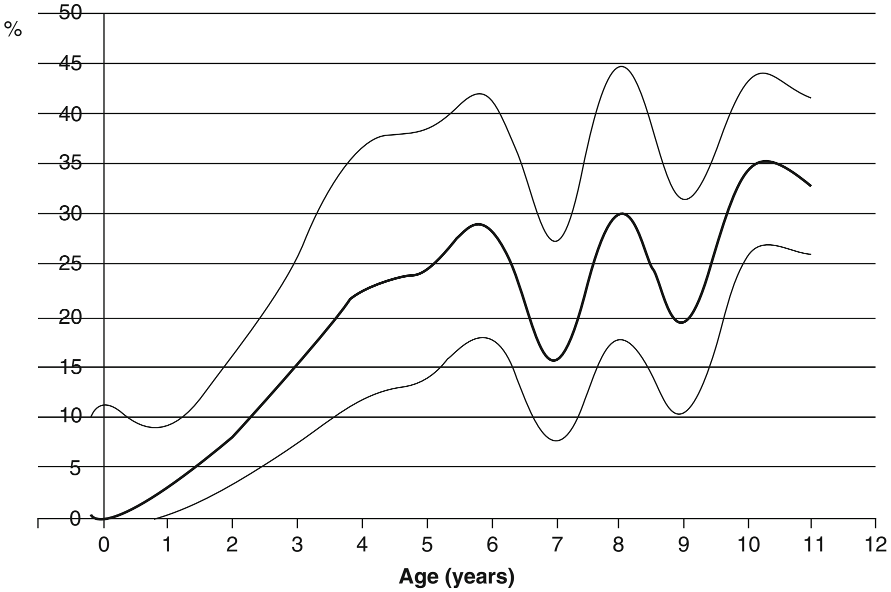

Fig. 10.1 The frequency of no germ cells in testicular biopsies at surgery in 862 consecutive cryptorchid boys <12 years at surgery for cryptorchidism (1,045 specimens) and 35 cryptorchid fetuses (70 specimens). Frequency and 95 % confidence limits shown (Cortes et al. 2007)

S-/T-values [21]. However, also possible abnormalities of the epididymal–testicular fusion may play a role in respect of the fertility potential, i.e. retention of sperm cells owing to possible absence of a connection between the testis and the epididymis or owing to obstruction in the male genital duct system. Ipsilateral epididymal abnormalities are associated with cryptorchidism, and the more cranial the UDT, the higher the incidence [22, 23]. An obstruction may also be acquired in connection with orchidopexy or infections. Thus, short-term results of orchidopexy (deferential duct lesions and testicular atrophy) also have an impact on later fertility.

Fertility is definitely related to the characteristics of the UDT at orchidopexy in childhood (Table 10.1). Men who had orchidopexy because of bilateral cryptorchidism are more affected than unilateral cases. However, the position of the testes at time of orchidopexy is also important. No fertility has been reported in men who underwent bilateral abdominal orchidopexy in childhood [5]. This is in agreement with the fact that these testes have most severely impaired germ cell number [1, 24]. In an analysis of larger cohorts of adult men who underwent bilateral inguinal orchidopexy in childhood, Lee and Coughlin [25] found that 35 % (95 % CL: 29–52 %) did not achieve paternity in 1 year. This figure is in accordance with the findings of Cortes et al. [21] that 54 % (95 % CL: 42–66 %) were infertile according to semen and hormonal analysis. In a review of 15 studies of men who had bilateral orchidopexy in childhood, only 21 % of 323 men had at least 20 million sperm cells/ml in the ejaculate, which according to the WHO at time of the review was the lower limit of the normal range [26].

Table 10.1 Prognosis for fertility in UDT after orchidopexy according to semen analysis +/− hormonal profile

Authors	No. of patients	Age at operation (years)	Percentage 'fertile' unilateral	bilateral
Werder et al. (1976) [17]	37	11	96	29
Hadziselimovic et al. (1984) [20]	24	7–14	77	17
Puri and O'Donnell (1988) [50]	142	7–13	74	30
Singer et al. (1988) [51]	25	6	70	40
Cortes et al. (1996) [15]	132	10–16	71	16
Taskinen et al. (1996) [27]	22	1–3	100	100
Taskinen et al. 1996 [27]	29	4–12	82	14
Engeler et al. (2000) [28]	14	<2	–	46

According to the histopathological studies it is assumed that orchidopexy at an early age improves the likelihood of eventual fertility. This is confirmed by data from two studies showing that orchidopexy in bilateral cryptorchidism led to a normal sperm count in 76 % of the men if surgery was performed between 10 months and 3 years of age, compared to 26 % following surgery between 4 and 14 years of age [27, 28]. Feyles et al. [29] have later shown that normal total sperm count was found in 26 (96.3 %) of 27 young men surgically treated for cryptorchidism within the first year of life, compared to 18 (75.0 %) of 24 men surgically treated in their second year. This difference was significant. Normal sperm motility in the two groups was found in 96.3 % versus 66.7 %, respectively ($p = 0.008$).

However, though important, early surgery is probably not enough to assure normal fertility in all cases, as other factors are involved. In 40–70 % of the patients with bilateral cryptorchidism becoming infertile, a prepubertal hypothalamic–pituitary–gonadal hypofunction is probably involved in the impaired maturation of germ cells leading to infertility, despite early orchidopexy [19, 30]. Fetal environmental factors, such as maternal heavy smoking during pregnancy, may also influence the fertility potential in cryptorchidism [31]. Storgaard et al. [32] reported that sons of mothers who smoked more than ten cigarettes per day during pregnancy had reduced sperm density, total sperm count, and inhibin-B and elevated FSH [32]. Others have later reproduced their results, also showing smaller testis size among men exposed to smoking in utero [33].

In unilateral cryptorchidism the risk of infertility in adulthood is not so dramatically increased as in the bilateral cases. Lee et al. [34] found that 10 % (95 % CL: 5–15 %) of men operated in childhood for unilateral cryptorchidism did not achieve paternity in 1 year compared to 5 % in a control group. This figure is in accordance with the findings of Cortes et al. [21] that 9 % (95 % CL: 3–19 %) were infertile according to semen and hormonal analysis. In a review of 14 studies of men who had unilateral orchidopexy in childhood 70 % of 747 men had at least 20 million sperm cells/ml in the ejaculate, which according to the WHO at time of the review was the lower limit of the normal range [18]. That means that there is an effect on fertility in unilateral orchidopexy as only 49 % adults with persistent unilateral cryptorchidism had at least 20 million sperm cells/ml in the ejaculate [18]. So also in unilateral cases there is a fertility problem. This is in accordance with the histopathological studies showing that in a proportion of cases with unilateral cryptorchidism there is evidence of a bilateral disease [19]. In patients with no germ cells in the UDT at time of surgery, 33 % ended up being infertile according to semen and hormonal analysis, even though the contralateral testis was descended [21]. In a follow-up on 91 patients Kraft et al. [35] found that total germ cell numbers on histopathology at the time of orchidopexy was not associated with significant changes in hormone levels or semen analysis results in adulthood. Testis biopsy at orchidopexy seemed to be limited in predicting future fertility in unilateral UDT but more clinically useful in predicting fertility potential for those with bilateral UDT. It must be emphasised that this report actually showed a significant association between abnormal number of adult dark spermatogonia per tubular transverse section and decreased sperm density. The figures were 38 % (20 of 52) in unilateral and 80 % (12 of 15) in bilateral cryptorchidism. Increased FSH was reported in the formerly unilateral cryptorchid cases with abnormal number of adult dark spermatogonia per tubular transverse section (AdS/T). A normal number of adult dark spermatogonia per tubular transverse section was associated with a normal sperm density in 88 % (29 of 33) of unilateral and 100 % (2 of 2) of bilateral cases. These results were in accordance with previous reports [19].

In addition to the fertility parameters in the present review it has to be mentioned that the fertility prospects are greatly improved with advent of sperm extraction and intracytoplasmic sperm injection techniques [5].

10.3.2 Retractile and Ascending Testes with Acquired UDT

Few studies have addressed the subsequent fertility of boys with retractile testes. Rasmussen et al. [16] observed a cohort of 545 boys with UDT over a number of years. Ninety-one of these boys had bilateral ‘UDT’ which were not operated upon and which descended spontaneously into the scrotum after 10 years of age. When they were greater than 18 years of age, 45 of these young men were investigated for their fertility status. They had significantly decreased testicular volumes, and their sperm counts were below the lower limit of the normal range. The authors concluded that UDT which undergo spontaneous descent in adolescence have a significantly decreased potential for spermatogenesis, leading to relatively decreased fertility. In retrospect, it is not possible to know whether these boys had what might now be called ‘retractile’ or ‘ascending’ testes. However, since most surgeons think that a congenital UDT would never descend into the scrotum, it is quite likely that this is an intermediate group. These testes have been classified as either ‘ascending’ or ‘retractile’ testes by different authors, making exact classification controversial. However, whatever their classification would be in current terminology, they do show that spontaneous descent of the testis at puberty does not protect the child from subsequent decreased fertility in adult life. An important conclusion to be reached from this study is that any testis which does not remain in the scrotum during childhood may suffer secondary degeneration regardless of its aetiology. This would be consistent with surgically created cryptorchidism in animal studies where secondary degenerative changes occur which are very similar to that seen in the human [36].

Agarwal et al. [37] retrospectively reviewed the charts of 122 boys (mean age 5.4 years) who were referred for a suspected UDT and were found to have a retractile testis. A retractile testis was defined as a suprascrotal testis that could be manipulated easily into the scrotum and remained there without traction until the cremasteric reflex was induced. The boys were followed by annual examinations, to demonstrate the presence of retractile, descended (non retractile) testes or UDT and the presence or absence of a taut or inelastic spermatic cord. Of 204 retractile testes 61 (30 %) descended (became non retractile), 66 (32 %) became UDT, and 77 (38 %) remained retractile. Of the 62 retractile testes with a taut or inelastic spermatic cord, 35 (56 %) became UDT. Boys in whom UDT developed were a mean of 4.9 years old. The authors concluded that a retractile testis is not a normal variant given the associated 32 % risk of becoming an ascending or acquired UDT. In a study by Van Brakel et al. [38] andrological evaluation including paternity, scrotal ultrasound, reproductive hormones, and semen analysis was performed in three groups: men with ascending UDT, healthy controls, and men with previously congenital UDT. In comparison with controls, men with ascending UDT more often had significantly abnormal testicular consistency, smaller testes, lower sperm concentration, and less motile sperm. Except for more often a normal testicular consistency in men with ascending UDT, no differences were found between men with ascending UDT and men with congenital UDT. Also, no differences were found between men with ascending UDT which had spontaneously descended and men who underwent orchidopexy. However, fertility potential is still unknown for men who had immediate surgery at diagnosis of ascending UDT earlier in childhood, and this is a subject for future studies.

10.4 Malignancy

Testicular cancer is the most common cancer in men aged 20–34 years, and cryptorchidism is the key accepted risk factor carrying a relative risk between 3.7 and 7.5 times higher than the background population [5, 39–41]. Statistically 5–10 % of testicular cancers are associated with cryptorchidism [41–43]. Testicular maldevelopment or de-differentiation is identified in a large fraction of men with testicular cancer and intratubular germ cell neoplasia (ITGCN) [40, 44]. ITGCN (also known as carcinoma in situ) is a histological premalignant pattern that can be seen in cryptorchid testis in early childhood. In a review of 6 studies on 2,800 prepubertal testicular biopsies from cryptorchid testes, ITGCN neoplasia was seen in 0.36 % [18]. In a study by Cortes et al. [21] ITGCN was found in 4 % (7/182) of patients with intra-abdominal testes, abnormal external genitalia, and/or abnormal karyotype (45,X/46,X del Y (q21) and 46,XY/47,XYY) but in none of 1,281 patients in the rest of the cryptorchid cohort. This means that patients with intra-abdominal testes, abnormal external genitalia, and/or abnormal karyotype may be of special risk in development of cancer, and biopsy is recommended at orchidopexy, but only 0.5 % of the total material had ITGCN. According to the aforementioned data, ITGCN must then be present in far less than 10 % of prepubertal cryptorchid testes later developing cancer in adulthood. This is because, according to the results of a cohort study of adults with cryptorchidism treated in childhood from the same area as the previous mentioned studies, the incidence of testicular cancer was estimated to be 6.1 % [45]. The high risk of ITGCN in the intra-abdominal testes was confirmed in a series of testicular biopsies at evaluation of 190 21–59-year-old infertile men with a history of cryptorchidism. Six of 190 (3.2 %) men had ITGCN, all 6 with a history of intra-abdominal cryptorchidism [46].

The risk of developing testicular cancer in cryptorchid men has not been eliminated by orchidopexy, but it appears to decrease the risk [41, 44, 47]. In the epidemiological studies of testicular germ cell cancer in 514 cases and 720 controls by Moller [41], an increased cancer risk associated with cryptorchidism was found to be higher in bilateral than in unilateral cryptorchidism (OR: 4.9 and 2.9 respectively). Of the 21 cases with unilateral cryptorchidism, the cancer occurred in the ipsilateral UDT in 14 cases and in the normally descended (contralateral) testis in 7 cases. The relative cancer risk was therefore 3.9 in the ipsilateral and 1.9 in the contralateral testis. This also supports the finding that in some cases unilateral cryptorchidism may be a bilateral disease, thus carrying a risk of bilateral neoplasia. Another interesting finding of this large case/control study was that the younger the boy was at operation, the lower the odds ratio (OR) for later testicular cancer. For boys 0–9 years at surgery OR: 1.1, for boys 10–14 years at surgery OR: 2.9, for boys more than 15 years at surgery OR: 3.5, and adults with persisting cryptorchidism OR: 14.4 [41]. The similar trend was seen in a recent Swedish follow-up study on almost 17,000 operated cryptorchid patients. For boys 0–6 years at surgery OR: 2.02, for boys 7–9 years at surgery OR: 2.35, for boys 13–15 years at surgery OR: 5.06, and for boys 16–19 years at surgery OR: 6.24 [48]. In a meta-analysis of the problem published by Walsh et al. [47], they saw the same trend and concluded the following: in males with cryptorchidism, prepubertal orchidopexy may decrease the risk of testicular cancer. While preservation of fertility and self-examination are important, this indication is equally important for early surgical intervention. There are actually few studies in this meta-analysis, including the study by Moller [41] previously presented, but not the Swedish study. The OR of testicular cancer in the contralateral descended testis in unilateral UDT in the study by Moller [41] was 1.9, and in the study by Swerdlow et al. [49] it was 2.1.

Conclusion

Operative success for cryptorchidism, defined as a testis permanently placed in the scrotum without atrophy, can be achieved for at least 90 % of testes that were originally distal to the external inguinal ring, for at least 85 % of ‘true’ inguinal (i.e. canalicular) testes and for approximately 80 % of intra-abdominal testes.

There is good short-term evidence that early operation is likely to decrease the risk of the two major long-term sequelae: infertility and malignancy. However, there is little long-term evidence yet of improved prognosis for fertility and malignancy risk because of the length of time between initial treatment and ultimate result (i.e. 20 years for fertility and 30–40 years for malignancy). Nevertheless, the improved short-term outcomes for early orchidopexy less than 1 year of age suggests that further improved results should be seen in future years, as more patients having orchidopexy in early infancy reach adulthood.

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Conclusions and Future Developments

11

Testicular descent and undescended testis (UDT) remain enigmas, although our understanding of both these processes has advanced considerably in the last few years.

A look at the evolution of testicular descent demonstrates that mammals have developed widely different anatomical solutions to the problem of storing cool spermatozoa. In particular, the site, form, and physiology of the scrotum differ dramatically, yet most species show evidence of specific adaptations towards decreased gonadal and epididymal temperature. Our original aim in reviewing the evolutionary aspects was to see if testicular descent could be divided into two separate phases, analogous to those seen in humans and laboratory animals. We hypothesised that if the two steps were under different endocrine controls, this should be evident in their evolution because different mechanisms should evolve independently and probably separately in time. Not surprisingly, the evidence was a little too complex to confirm this suggestion outright, although there was a definite trend towards two separate steps. Importantly, the link between the genitofemoral nerve and gubernaculum with the breast bud in marsupials has enabled a similar link to be discovered in eutherian mammals.

Historical review of research done years ago proved to be a revelation, and the reader is urged to read these old papers directly, rather than rely on poor quality and inaccurate secondary sources. Hunter's description [1] is a landmark description of the gubernaculum that is still relevant today. The 'Tails of Lockwood' are never mentioned in Lockwood's original paper 1888, but were thrust upon him by later writers [2]. Lockwood merely speculated that they may exist, without providing any direct evidence, and now that we know that the gubernaculum migrates to the scrotum in the inguinoscrotal phase, the 'Tails of Lockwood' can be consigned to history.

Perhaps the most revealing studies are the clear anatomical descriptions of the migration of the gubernaculum from the inguinal canal to the scrotum [3]. The importance of this migration phase has been forgotten and/or ignored for most of

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the twentieth century and had to be ‘rediscovered’, first by Backhouse [4] and then by Heyns [5] and more recently by [6]. Its key role in descent can be appreciated when one considers that the human gubernaculum is about 1 cm in diameter (just before the start of inguinoscrotal migration), yet the distance to the bottom of the scrotum is 4–5 cm. With such a long distance to travel, we should be wondering why scrotal descent occurs at all, rather than why UDT is common (Fig. 11.1).

The first phase of testicular descent occurs between about 10 and 15 weeks of gestation and is caused by growth and enlargement of the gubernaculum, described by Wensing in 1973 [7] as the swelling reaction. This growth of the male gubernaculum (with a short cord) anchors the testis close to the inguinal region as the fetus grows; in the female the lack of an enlarged gubernaculum and its elongation allows the ovary to remain near the lumbar region during fetal growth. As the ovary recedes from the inguinal region, the gubernaculum becomes elongated and thin, later to become the ligament of the ovary and the round ligament. Although the ovary in the human ends up lying quite near the internal inguinal ring, the pathway of the round ligament reveals that in embryological terms the female gonad is distant from the inguinal canal, despite the frequency of inguinal hernias in females containing the ovary. Unlike other animals that have a thin bicornuate uterus and perinephric ovaries, the human female has a short, solid uterus and pelvic ovaries: differences in the degree of Müllerian duct fusion and uterine growth probably account for the lower position of the human ovary compared with many other mammals (Fig. 11.2).

Transabdominal migration of the testis occurs at a different time and under different hormonal control than later inguinoscrotal descent. Animal models suggest not only that gubernacular swelling (and hence transabdominal descent) is independent of androgens, but also that shortening of the gubernacular cord in humans may be regulated by AMH. However, the main hormone controlling the swelling reaction is INSL3.

In Chap. 3, we show how inguinoscrotal descent is controlled by androgens indirectly via the GFN, and the androgens must first act on the nerve. Androgens are important in a brief ‘programming’ window (E15–E19 in rats), where the GFN is masculinised and the inguinoscrotal fat pad is remodelled to initiate and support gubernacular migration to the scrotum.

The precarious migration undertaken by the gubernaculum may be directed by the nerve, leading us to speculate that undescended testes (UDT) may be caused by any process interfering with the complex morphological process. The anatomy and physiology of the GFN still needs extensive study to determine its true role. The neurotransmitter we have identified in the rodents, calcitonin gene-related peptide (CGRP), has been shown to be a possible ‘second messenger’ for androgens acting on the gubernaculum in humans, as exogenous CGRP can trigger obliteration of the patent PV of an inguinal hernia in vitro. One day it may be possible to use exogenous CGRP to treat UDT in children and lead to an entirely new way to induce testicular descent nonsurgically, as we have shown already this is possible in piglets with congenital UDT [9].

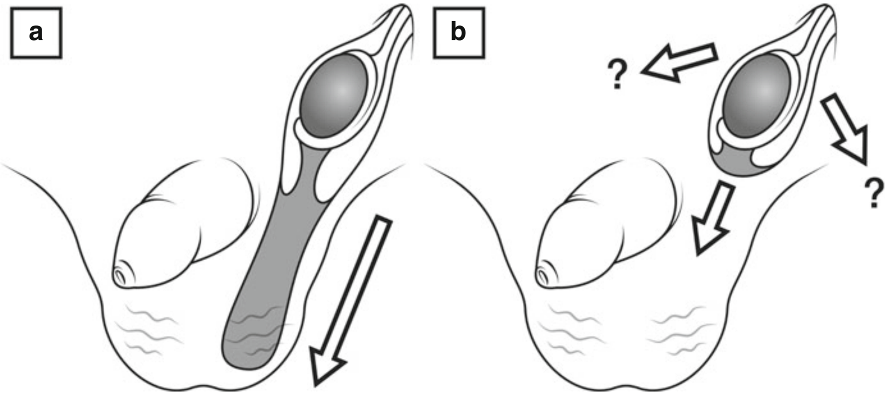

Fig. 11.1 (**a**) Schema of how many clinicians have viewed testicular descent, with the gubernaculum connecting the testis directly to the scrotum: descent seems a foregone conclusion and cryptorchidism a mystery. This incorrect view arose because the gubernaculum becomes secondarily attached to the scrotum after descent is complete. (**b**) The actual process of migration of a small gubernaculum across the groin is a precarious step which is not automatic: cryptorchidism seems, if not inevitable, at least not unexpected. Obviously there needs to be a mechanism to allow migration towards the scrotum; our postulate is that the genitofemoral nerve fulfills this role

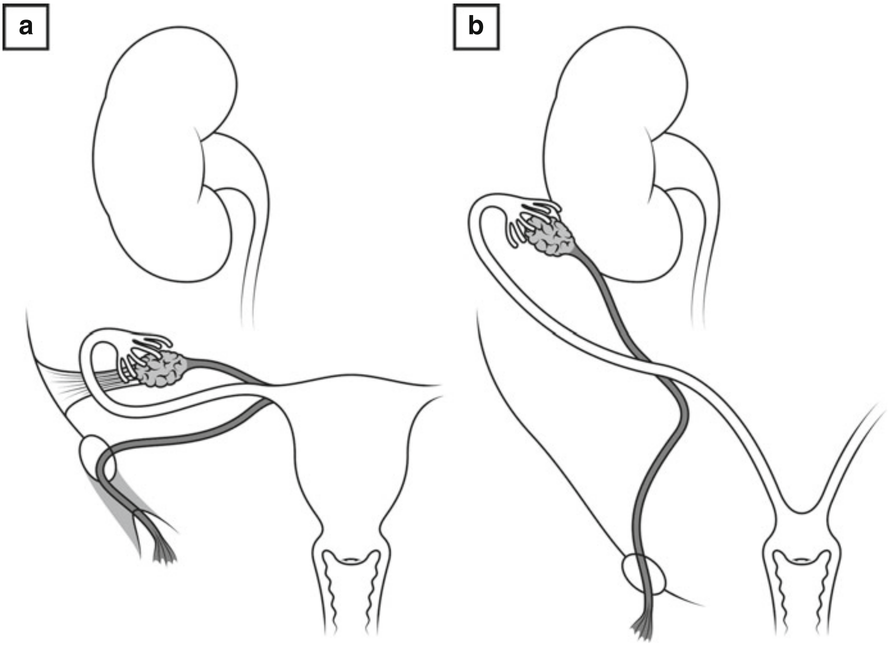

Fig. 11.2 Diagram demonstrating the different position of the ovary in (**a**) humans and (**b**) rodents and its relation to the development of the uterus (U). Despite the proximity of the human ovary to the internal inguinal ring, the gubernacular ligaments are not foreshortened as in the male (Reproduced with permission from Hutson et al. [8])

Now that we are beginning to understand the complex remodelling of the inguinoscrotal tissues to allow the second phase of testicular descent, we can start to put the different aberrations of the process into perspective. As the gubernaculum must migrate from the inguinal abdominal wall to the scrotum, congenital UDT will result from failure of this process. After the testis reaches the scrotum the PV must close, but failure of this will cause inguinal hernia/hydrocele. Finally, not only must the PV close after descent (too prevent hernia), but also it must undergo complete apoptosis to allow the vas deferens and testicular vessels to grow in proportion to the adjacent tissues. Failure of this process is likely to be a common cause for acquired/ascending testes (Fig. 11.3).

In discussing the classification of UDT, it is the testis in the superficial inguinal pouch that is the most difficult to understand. By comparison, it is straightforward to imagine that testes arrested in the line of descent have a putative primary deficiency of androgens and ectopic testes have migrated to the wrong place (? secondary to a misplaced GFN). The superficial inguinal pouch does not appear to be

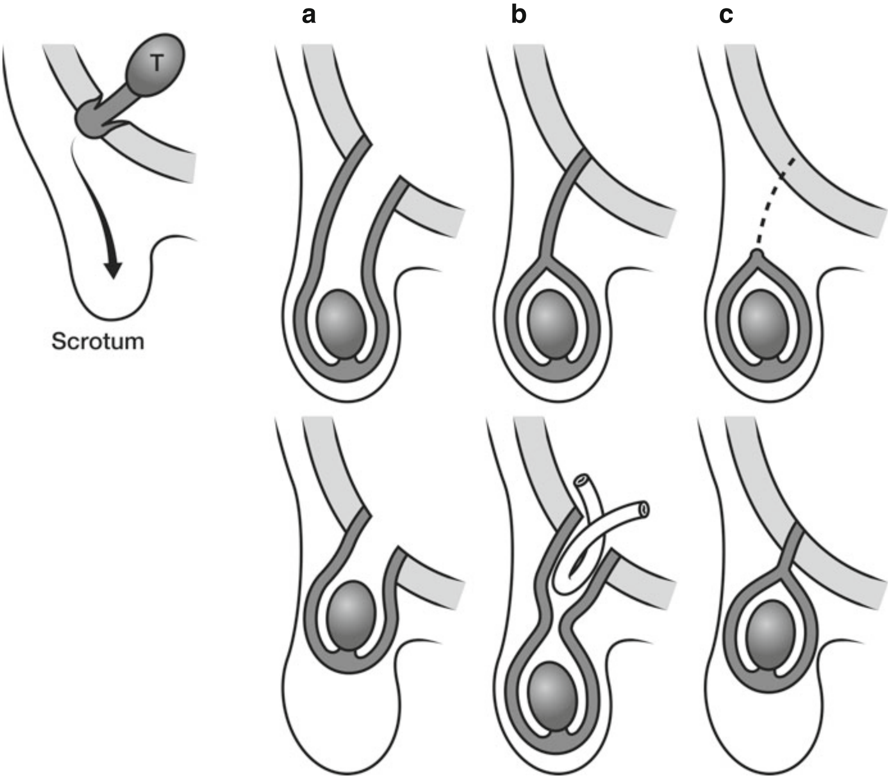

Fig. 11.3 Schema showing how the gubernaculum migrates to the scrotum from the groin to the inguinoscrotal phase. (**a**) If migration is faulty, congenital UDT results. (**b**) If failure of PV closure occurs, inguinal hernia results. (**c**) If the obliterated PV fails to completely disappear (by ? apoptosis or remodelling), the remaining fibrous remnant may cause an acquired, ascending testis

'ectopic' and yet it is off the line of descent. At surgery, the gubernaculum in these cases usually is attached just outside the neck of the scrotum, perhaps secondary to failure of the GFN to reach the scrotum. The lateral displacement of the testis and PV may well be a passive result of physical pressure or alternatively may be forced upon the testis because of a fascial barrier preventing its entry into the scrotum: further research is needed to resolve these possibilities.

The 'retractile' testis is another dilemma, creating a major controversy over whether it is normal or abnormal. The criteria devised by Wyllie [10] imply that some retractile testes are abnormal, and it now appears that 'retractile' testes form a grey zone between descended testes and those that have developed into acquired UDT. This apparent heterogeneity complicates clinical decision-making enormously. The cause of retractile testes is unknown, but their response to hormone (LHRH or hCG) treatment suggests a partial deficiency of androgens. Much fruitful knowledge about this common clinical problem should come out of longitudinal follow-up studies, such as have been done recently in the Netherlands [11–14]. There is an emerging view (supported by the authors) that 'retractile' testes represent testes that may be developing into acquired UDT.

Acquired UDT or 'ascending' testes are now well described. Although the testes are descended in infancy, with subsequent growth of the boy, the spermatic cord fails to elongate in proportion to body size, giving the impression that the testis is rising back out of the scrotum. At present, we remain ignorant of the cause, natural history, and prognosis for acquired UDT, and the need for treatment is controversial. A major new goal for the future is to categorise this variant precisely so that rational decisions can be made about whether and when treatment is required.

The high frequency of cryptorchidism is a concern, although the epidemiological explanation for this is obscure. Likewise, the causes of UDT remain largely unknown, although there are studies showing a link with poor placental function and possible maternal exposure to endocrine disruptors, including cigarette smoke [15].

For the otherwise normal boy with an UDT, the cause may be a combination of deficient androgens and local mechanical factors. We speculate that minor derangement of one GFN may cause the testis to remain in the groin, while true ectopic testes are likely to be secondary to an aberrant peripheral pathway of the GFN axons. Around 20 % of UDT may be associated with a primary gonadal (and hence hormonal) deficiency or defects in the hypothalamic–pituitary axis.

The effects of cryptorchidism are secondary to the abnormally high temperature experienced by the non-scrotal testis, which leads initially to physiological abnormalities (such as deficiency of postnatal secretion of testosterone, inhibin-B, and AMH) and later to morphological derangement. Macroscopic dysplasia with loss of germ cells and a five to tenfold increase in the cancer risk is the ultimate consequence, and these latter problems remain the primary reasons for offering treatment.

With the recent observations that germ cells are depleted during infancy, the recommended age for surgery has fallen stepwise to this age, with the hope that infertility and testicular cancer will be avoided in young adult life. These high hopes and ideals need to be kept in perspective although there is now mounting evidence that early gonocyte transformation and/or apoptosis is perturbed in UDT. The central dilemma facing clinicians dealing with cryptorchid infants is that definitive proof of benefits of early surgery is hard to obtain because of the lag phase between the initiation (on a large scale) of orchidopexy at 6–9 months of age and its long-term results in grown men. Nevertheless, the limited evidence available, from recent hormonal studies and ultrasound examination of the testis, is full of hope that repair in infancy will significantly improve the prognosis for the adult testis.

We describe the methods of clinical examination in detail in Chap. 7. The two most important points worth remembering about the physical examination, apart from it being difficult, are that to find an inguinal testis, the surgeon needs to know the bony landmarks (to identify the inguinal canal and superficial inguinal pouch) and recognise that the testis is mobile. Many a time have students proudly announced in the outpatient clinic that they have located an inguinal testis, only to be crestfallen when they realise that they have found an enlarged inguinal lymph node. Surprisingly, many people do not know that the UDT is extremely mobile within its undescended PV, making it hard to find unless one looks deliberately for something mobile. We give some useful criteria for distinguishing UDT from retractile testes, although even with simple criteria, the assessment can be difficult.

Investigation of impalpable testes is an interesting and controversial area, but laparoscopy is now the 'gold-standard' test to find the testis. Laparoscopic orchidopexy by a 1-stage or 2-stage method is the operation of choice for intra-abdominal testes. However, the recent description by Shehata et al. [16] of lengthening the testicular vessels needs to be assessed more fully, but is intriguing.

The open surgical technique of orchidopexy has not changed much in recent years, except for the more widespread use of the scrotal orchidopexy, especially in cases of acquired UDT. Simple internal fixation with either 'buttonholing' the testis through the scrotal fascia or lightly anchoring the testis to the midline septal tissues is the standard. Day surgery is effectively painless, with no painful premedication injection and local (cream) anaesthesia for induction of anaesthetic (to avoid 'the needle'), and regional analgesia for the operative site afterwards. Waterproof and effectively adherent dressings allow immediate bathing and to avoid external wound contamination, which is a significant risk because the patients are still in nappies.

Hormone treatment has waned in popularity in recent years with numerous clinical trials demonstrating poor efficacy except for retractile testes. It is a great irony, and a measure of the craving for better alternatives to surgery, that hormone therapy was pushed so hard for nearly 60 years, despite being based on a model of precocious puberty. Many reviews of hormone treatment cite Engle [17] as a landmark in the English literature, for showing that immature macaque testes could be induced to descend with crude pituitary hormone extracts. Few advocates realised that the macaque testis descends prenatally, then reascends after birth to the groin until puberty. Hormonal treatment merely induced secondary pubertal descent, analogous to that currently seen in retractile testes and acquired UDT.

The main roles for hormonal therapy in the future may be as a diagnostic test for retractile testes in older boys or as an adjunct to surgery in infants to stimulate germ cell maturation by supplementing an impaired transient hormonal surge in 'minipuberty'.

Determining the hormonal profile in blood samples and status of the germinative epithelium in testicular biopsies of cryptorchid boys may in the future facilitate identification of patients with high risk of infertility even though successful orchidopexy is carried out 6–9 months of age. For some of these patients adjuvant hormonal treatment may be an option. For others cryopreservation of testicular tissue may be indicated. So far we have reported our freezing protocol of testicular tissue in prepubertal boys yielding good structural integrity [18]. Promising results of restoration of fertility from cultured auto-donor stem cells have been achieved in animals. However, fertility restoration after cryopreservation has not yet been successful in human males.

The long-term outlook for a cryptorchid infant, if treated well, should be a significant improvement in fertility and reduction of cancer risk later in life. We will, however, be waiting for a few years yet before there are large clinical studies to support this optimistic view. The possibility of alternative therapies arising from the research described in Chaps. 2 and 3 remains uncertain: new understanding, however, should help us resolve the many unanswered questions about this fascinating clinical problem.

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